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2-[4-(1-Oxo-2-isoindolinyl)phenyl]propanoic acid (**1**) having a potent analgesic and anti-inflammatory activity could be obtained by three methods, which were found to provide extremely useful ways for the synthesis of **1** from the industrial point of view. (E)- and (Z)-Isomers of 2-butenoic acid and oxiranecarboxylic acid derivatives as the intermedaites in the synthesis of **1** were separated and characterized. Furthermore, the optical resolution of (±)-2-[4-(1-oxo-2-isoindolinyl)phenyl]propanoic acid was successfully achieved using cinchonidine as a resolution reagent.

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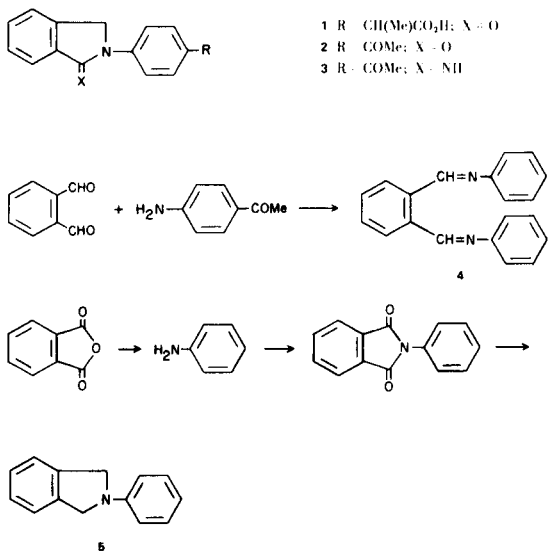
A number of phenylacetic and phenylpropanoic acid derivatives which possess antiinflammatory and analgesic activities have been reported (4). We have also investigated a new synthesis of these types of compounds in order to develop a new substance showing an effective activity. Now we wish to report three alternative syntheses of 2-[4-(1-oxo-2-isoindolinyl)phenyl]propanoic acid (**1**) (5) which has potent antiinflammatory and analgesic activities, the optical resolution of this compound **1**, the interesting information of geometrical isomers of 2-butenoic acids and stereoisomers of oxiranecarboxylic acids which were intermediates to **1**.

The synthetic plans for 2-[4-(1-oxo-2-isoindolinyl)-phenyl]propanoic acid (**1**) were designed by three routes, by which the objective compound was obtained. The starting material, 4-(2-oxo-2-isoindolinyl)acetophenone (**2**), was synthesized by four routes as follows: 1) condensation of 4-aminoacetophenone with ethyl 2-bromomethylbenzoate (6); 2) hydrolysis of 4-(1-imino-2-isoindolinyl)acetophenone (3) obtained by reaction of 4-aminoacetophenone with 2-cyanobenzyl bromide (5a); 3) condensation of 4-aminoacetophenone with *o*-phthalaldehyde followed by heating the resulting 4,4′-(*o*-phenylenebismethylene)diacetophenone (4) in acetic acid; 4) Friedel-Crafts reaction of *N*-phenyl-1-oxoisoindole (7), obtained from phthalic anhydride and aniline by fusion and subsequent reduction of the resulting *N*-phenylphthalimide (8) with zinc powder in acetic acid, with acetyl chloride.

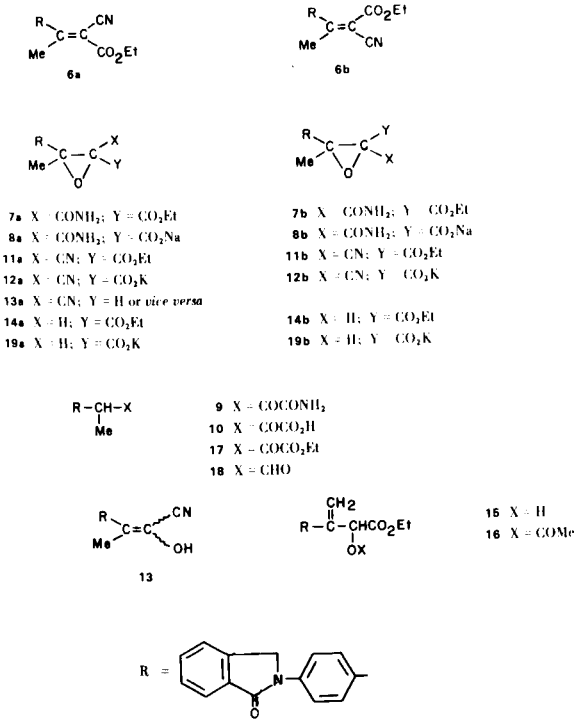
Scheme I



Since the starting material was available easily as mentioned above, we investigated the synthesis of 2-[4-(1-oxo-2-isoindolinyl)phenyl]propanoic acid (**1**) according to the following three routes.

Firstly, a Knoevenagel reaction of the acetophenone **2** with ethyl cyanoacetate in the presence of catalyst gave a geometrically isomeric mixture of ethyl (E)-2-cyano-2-[4-(1-oxo-2-isoindolinyl)phenyl]-2-butenoate (**6a**) and (Z)-form **6b**. Two kinds of catalysts, a mixture of ammonium acetate-glacial acetic acid and benzylamine-glacial acetic acid, were examined for this reaction. The latter was more effective for shortening the reaction time and the formation ratio of the compounds **6a** and **6b** in using this catalyst was 4 to 1 by its nmr spectral analysis *vide infra*. (E)-Isomer **6a** was separated by fractional recrystallization, and was oxidized with hydrogen peroxide in the presence of sodium phosphate according to Igarashi's method (9) to give a mixture of ethyl (E)-2-carbamoyl-3-methyl-3-[4-(1-oxo-2-isoindolinyl)phenyl]oxiranecarboxylate (**7a**) and (Z)-isomer **7b** in a ratio of 3 to 1 by its nmr spectral analysis *vide infra*. Both isomers were successfully separated by column chromatography on silica gel and multiple recrystallization. Treatment of both compounds **7a**, m.p. 220° dec., and **7c**, m.p. 197-198°, with ethanolic sodium hydroxide, followed by heating the resulting sodium salts **8a** and **8b** in acetic acid, afforded 2-oxo-3-[4-(1-oxo-2-isoindolinyl)phenyl]butanamide (**9**), m.p. 210-212°. Hydrolysis of the butanamide **9** using

Scheme 2



sodium hydroxide gave 2-oxo-3-[4-(1-oxo-2-isoindolinyl)-phenyl]butanoic acid (**10**). The butanoic acid **10** was converted to the objective 2-[4-(1-oxo-2-isoindolinyl)-phenyl]propanoic acid (**1**) by oxidation using hydrogen peroxide in sodium hydroxide solution. The melting point and physical data were completely identical with those of the authentic sample (5).

Secondly, oxidation of the ethyl 2-butenoate (**6a**) with a slightly excess of hydrogen peroxide in the presence of sodium hydrogen phosphate gave ethyl (E)-2-cyano-3-methyl-3-[4-(1-oxo-2-isoindolinyl)phenyl]oxiranecarboxylate (**11a**) and (Z)-isomer **11b** in a ratio of 2 to 1 by its nmr spectral analysis *vide infra*. Both isomers were successfully separated by chromatography on silica gel and recrystallization. Hydrolysis of ethyl oxiranecarboxylates **11a** and **11b** with potassium hydroxide solution, followed by acidification of the resulting potassium salts (**12**) with hydrochloric acid gave a geometrically isomeric mixture of 2-hydroxy-2-[4-(1-oxo-2-isoindolinyl)phenyl]-2-butenonitrile (**13**) which is a decarboxylated product of 2-cyano-3-methyl-3-[4-(1-oxo-2-isoindolinyl)phenyl]-oxiranecarboxylic acid. Since the 2-butenonitrile **13** was an unstable compound, **13** was subjected to hydrolysis with 20% sodium hydroxide solution without purification to afford the objective compound **1**. On the other hand, methanolysis of **13** gave the methyl ester of **1**. The fact shows that the structure should be **13**. Moreover, a Darzens reaction of the acetophenone (**2**) with chloroacetonitrile gave 3-methyl-3-[4-(1-oxo-2-isoindolyl)-phenyl]oxiranecarbonitrile (**13a**), whose physical data were different from those of **13**. On the basis of this experiment, the structure of the compound obtained from acidification of the salts (**12**) was the 2-butenonitrile (**13**) and not **13a**.

Thirdly, a Darzens reaction of the acetophenone **2** with ethyl chloroacetate in tetrahydrofuran gave ethyl (E)-3-ethyl-3-[4-(1-oxo-2-isoindolinyl)phenyl]oxiranecarboxylate (**14a**) and (Z)-isomer **14b**, both of which were separated by chromatography on silica gel in a ratio of 2.4 to 1 and treated with concentrated hydrochloric acid and acetic acid to give the 2-oxobutanoic acid **10**. It is likely that ethyl 2-oxo-3-[4-(1-oxo-2-isoindolinyl)phenyl]butanoate (**17**) is initially formed *via* carbonium ion by acid-catalysed ring opening of oxirane and then transforms into **10** by hydrolysis. 2-[4-(1-Oxo-2-isoindolinyl)phenyl]propanal (**18**) was also isolated from the reaction mixture, during the reaction of which a saponification of ester group would occur prior to the opening of oxirane ring, followed by decarboxylation. This fact was supported by the result that the potassium salts **19a** and **19b** obtained from **14a** and **14b** by hydrolysis with potassium hydroxide were easily decarboxylated by acidification with hydrochloric acid.

On the other hand, heating **14a** and **14b** in dry xylene saturated with dry hydrogen chloride or in glacial acetic acid gave ethyl 2-hydroxy-3-[4-(1-oxo-2-isoindolinyl)-phenyl]-3-butenoate (**15**) or 2-acetoxy derivative **16**, respectively. Under anhydrous conditions, opening of oxirane ring would be affected by hyperconjugation due to methyl group at the 4-position to yield the alcohol **15** or the acetoxy derivative **16**. Treatment of **14a** and **14b** with dry hydrogen chloride in xylene or in glacial acetic acid for a long time as described in an experimental section afforded **17**, whose phenomena suggested that the latter compound was formed by an isomerization and/or hydrolysis of the initially formed **15** and **16**. In fact, the nmr spectral analysis at a short reaction time in the synthesis of **17** from **14a** indicated the presence of the alcohol **15** or the acetoxy derivative **16** as the main product in the reaction mixture. The α-ketocarboxylate **17** was converted to 2-oxo-3-[4-(1-oxo-2-isoindolinyl)phenyl]butanoic acid (**10**) by hydrolysis with 10% aqueous sodium hydroxide solution.

Decarboxylation of the oxiranecarboxylic acids **8a**, **8b**, **12a**, **12b**, **19a** and **19b** would be most likely to occur in a concerted manner (10) rather than through the stepwise mechanism of decarboxylation followed by fragmentation of oxirane ring.

As mentioned above, antiinflammatory and analgesic 2-[4-(1-oxo-2-isoindolinyl)phenyl]propanoic acid (**1**) was successfully prepared by three routes. These procedures could be performed with no trouble to separate a geometrically isomeric and stereoisomeric mixture from the acetophenone **2** to the propanoic acid **1** in good yields

Scheme 3

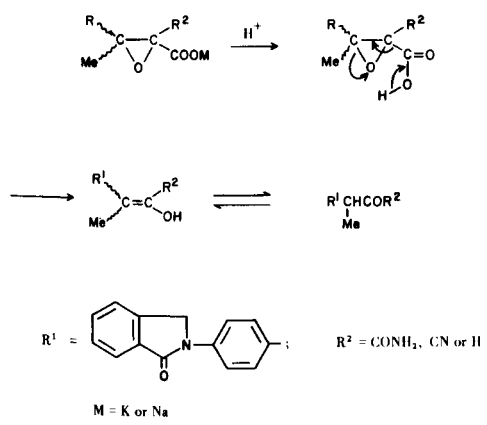


Table I

Chemical Shifts (δ) for 2-Butenoates and Oxiranecarboxylates

Compound No.	Configuration	CH_2	CH_3
6a	E	4.38	1.40
6b	Z	4.17	1.20
7a	E	4.37	1.32
7b	Z	3.90	0.87
11a	E	4.44	1.40
11b	Z	4.04	1.04
14a	E	4.31	1.34
14b	Z	4.03	1.00

through three routes and therefore these reactions provide a valuable method from the industrial point of view.

The chemical shifts in the nmr spectrum of isomers of the butenoic acids **6a** and **6b** and oxiranecarboxylic acid derivatives **7a**, **7b**, **11a**, **11b**, **14a** and **14b** are summarized in Table I. The signals of the ethyl group in the ester of the (Z)-form are shielded to a higher field than that of the (E)-form. The same phenomena were also reported by Valente (11).

On consideration of the formation ratio of geometrical isomer and stereoisomer, a Knoevenagel condensation of the acetophenone **2** with ethyl cyanoacetate and a Darzens condensation of **2** with ethyl chloroacetate were controlled by stability of transition state to yield mainly (E)-form.

Finally, the optical resolution of the propanoic acid **1** was performed using cinchonidine in ethanol to afford the crystalline cinchonide salt of (+)-2-[4-(1-oxo-2-isoindolinyl)phenyl]propanoic acid. Usual treatment of the mother liquor gave (-)-salt by recrystallization of a solid, obtained after evaporation of the ethanol, from isopropanol. Both (+) and (-)-salts were treated with hydrochloric acid to yield crystalline (+)-2-[4-(1-oxo-2-isoindolinyl)phenyl]propanoic acid, m.p. 205-207°, $[\alpha]_D^{20}$ = + 48° (c = 0.05 in dimethyl sulfoxide) and (-)-2-[4-(1-oxo-2-isoindolinyl)phenyl]propanoic acid, m.p. 205-207°, $[\alpha]_D^{20}$ = -48° (c = 0.05 in dimethyl sulfoxide).

Examination of antiinflammatory and analgesic activities and toxicity of the optically active compound **1** and its intermediates is now under investigation.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were measured with a Hitachi 215 spectrophotometer, nmr spectra with a JNM-PMX-60 spectrometer using tetramethylsilane as an internal reference and mass spectra with a Hitachi RMU-7 spectrometer.

4-(1-Oxo-2-isoindolinyl)acetophenone (**2**).

(a) A mixture of ethyl *o*-bromomethylbenzoate (2.43 g.) and 4-aminoacetophenone (4.59 g.) in ethanol (40 ml.) was refluxed for 4 hours. After cooling, the resulting precipitate was collected, washed with ether, dried and recrystallized from benzene-chloroform to afford **2** (2.26 g., 90%) as pale yellow needles, m.p. 243-244°; ir ν max (potassium bromide): 1700 (C=O) and 1660 cm^{-1} (C=O); nmr δ (deuteriochloroform): 2.60 (3H, s, CH_3), 4.93 (2H, s, $CH_2N<$), 7.5-8.2 (8H, m, ArH); ms: m/e 251 (M^+).

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.25; H, 5.24; N, 5.61.

(b) A mixture of 2-cyanobenzyl bromide (1.96 g.) and 4-aminoacetophenone (1.53 g.) in ethanol (40 ml.) was refluxed for 8 hours. After cooling, the resulting precipitate was collected, washed with ether and dried to give the hydrobromide of 4-(1-imino-2-isoindolinyl)acetophenone **3** (2.95 g., 89%), whose recrystallization from ethanol afforded colorless needles, m.p. 292-295° dec.; ir ν_{max}^{+} (potassium bromide): 1686 (C=O) and 1660 cm^{-1} (C=NH).

Anal. Calcd. for $C_{16}H_{15}BrN_2O$: C, 58.01; H, 4.56; N, 8.46. Found: C, 57.83; H, 4.41; N, 8.68.

To a solution of the above hydrobromide of **3** (0.99 g.) in ethanol (20 ml.) was added a solution of potassium carbonate (1.66 g.) in water (12 ml.) and the resulting mixture was refluxed for 24 hours. The solvent was evaporated off and the residue was taken up in chloroform, whose extract was washed with water and dried over magnesium sulfate. After evaporation of the solvent, the residue was recrystallized from benzene-chloroform to afford pale yellow needles (0.68 g., 80% from 2-cyanobenzyl bromide), m.p. 243-244°, identical with the above sample of **2** by comparison of the ir and nmr spectra and by tlc behavior.

(c) To a solution of 4-aminoacetophenone (2.7 g.) in dimethylformamide (20 ml.) was added dropwise a solution of *o*-phthalaldehyde (1.34 g.) in dimethylformamide (10 ml.) and the mixture was stirred at 60° for 2 hours. The reaction mixture was poured onto crushed ice and the resulting precipitate was collected and recrystallized from ethanol to give 4,4'-(*o*-phenylenebismethyleneimino)diacetophenone **4** (3.0 g., 82%) as yellow needles, m.p. 195-196°; nmr δ (deuteriochloroform): 2.60 (3H, s, CH_3), 2.67 (3H, s, CH_3), 5.03 (2H, s, CH x 2), 6.7-8.3 (12H, m, ArH).

Anal. Calcd. for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 77.88; H, 5.54; N, 7.10.

A solution of the above diacetophenone **4** (1.0 g.) in acetic acid (5 ml.) was refluxed for 4 hours. Removal of the solvent, followed by recrystallization of the resulting solid from benzene-chloroform, afforded pale yellow needles (0.6 g.) (88% from **4**), m.p. 243-244°, identical with the above sample of **2**.

(d) A mixture of phthalic anhydride (19 g.) and aniline (14 g.) was heated at 140-145° for 50 minutes. The resulting solid was triturated with water (50 ml.), filtered and washed with 10% potassium carbonate solution (50 ml.) and water (100 ml.) to

afford a colorless powder (28 g., 97%). This was recrystallized from acetic acid to give colorless needles, m.p. 214-215° (lit. (7), m.p. 208°). A stirred suspension of the phthalimide (100 g.), Zn powder (147 g.), and acetic acid (700 ml.) was heated under reflux for 5.5 hours. After removal of the insoluble substance by filtration, the filtrate was condensed to give a solid (72 g., 78%) which was recrystallized from benzene to afford colorless leaves, m.p. 166-167° (lit. (8) m.p. 158-160°).

To a stirred suspension of the oxoisoindole (**5**) (20.9 g.) in carbon disulfide (400 ml.) was added acetyl chloride (13.3 g.) and then aluminum chloride (39.9 g.) was added in small portions. The mixture was heated under reflux for 10 hours, the solvent was removed by decantation and the resultant red oil was poured into 10% hydrochloric acid (300 ml.) under ice-cooling. The precipitate was collected by filtration, washed with water and dried to give crystals, which were recrystallized from benzene-chloroform to give pale yellow needles (20.6 g., 82%), m.p. 243-244°, identical with the above sample of **2**.

Ethyl (E)- and (Z)-2-Cyano-3-[4-(1-oxo-2-isoindolinyl)phenyl]-2-butenoate (**6a**) and (**6b**).

A mixture of **2** (20 g.), ethyl cyanoacetate (15 g.), benzylamine (5 g.), glacial acetic acid (10 ml.) and benzene (200 ml.) was refluxed for 15 hours using a Dean-Stark apparatus. The benzene solution was washed with water, dried over sodium sulfate and evaporated to give a mixture of **6a** and **6b** (**6a**:**6b** = 4:1), which was recrystallized from ethanol to afford a mixture of **6a** and **6b** (21 g., 76%). Repeated recrystallization of the above mixture from ethanol gave **6a** as yellow needles, m.p. 163-165°; ir ν max (potassium bromide): 1720 (C=O) and 1690 cm^{-1} (C=O); nmr δ (deuteriochloroform): 1.40 (3H, t, J = 7 Hz, CH_2CH_3), 2.72 (3H, s, CH_3), 4.38 (2H, q, J = 7 Hz, CH_2CH_3), 4.90 (2H, s, $CH_2N<$), 7.2-8.3 (8H, m, ArH).

Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.62; H, 5.23; N, 7.89.

The ethanolic mother liquor was evaporated to give a mixture of **6a** and **6b**; nmr δ (deuteriochloroform): 1.20 and 1.40 (3H, double t, J = 7 Hz, CH_2CH_3), 2.60 and 2.72 (3H, double s, CH_3), 4.17 and 4.38 (2H, double q, J = 7 Hz, CH_2CH_3), 4.90 (2H, s, $CH_2N<$), 7.2-8.3 (8H, m, ArH).

Ethyl (E)- and (Z)-2-Carbamoyl-3-methyl-3-[4-(1-oxo-2-isoindolinyl)phenyl]oxiranecarboxylate (**7a**) and (**7b**).

A mixture of **6a** (3 g.), sodium phosphate tribasic dodecahydrate (0.8 g.), 28% hydrogen peroxide (10 ml.) and ethanol (30 ml.) was heated at 70° for 4 hours. After cooling the mixture was poured into ice water. The white solid precipitated was collected by filtration to afford a mixture of **7a** and **7b** (3.2 g., 97%) (**7a**:**7b** = 3:1), which was recrystallized from ethanol to give **7a** as colorless needles, m.p. 220°; nmr δ (dimethyl sulfoxide-d_6): 1.32 (3H, t, J = 7 Hz, CH_2CH_3), 1.70 (3H, s, CH_3), 4.37 (2H, q, J = 7 Hz, CH_2CH_3), 5.05 (2H, s, $CH_2N<$), 7.2-8.2 (8H, m, ArH).

Anal. Calcd. for $C_{21}H_{20}N_2O_5$: C, 66.30; H, 5.30; N, 7.37. Found: C, 66.22; H, 5.35; N, 7.62.

The ethanolic solution separated during the above recrystallization was evaporated and the residue was chromatographed on silica gel with chloroform to give **7b** as colorless needles, m.p. 197-198° (from 2-propanol); nmr δ (dimethyl sulfoxide-d_6): 0.87 (3H, t, J = 7 Hz, CH_2CH_3), 1.77 (3H, s, CH_3), 3.90 (2H, q, J = 7 Hz, CH_2CH_3), 5.05 (2H, s, $CH_2N<$), 7.2-8.2 (8H, m, ArH).

Anal. Calcd. for $C_{21}H_{20}N_2O_5$: C, 66.30; H, 5.30; N, 7.37. Found: C, 66.06; H, 5.13; N, 7.40.

Sodium (E)- and (Z)-2-Carbamoyl-3-methyl-3-[4-(1-oxo-2-isoindolinyl)phenyl]oxiranecarboxylate (**8a**) and (**8b**).

(a) To a solution of **7a** (380 mg.) in ethanol (24 ml.), 3% (w/w) ethanolic sodium hydroxide (2.8 ml.) was added and the mixture was heated at 70° for 2 hours. The resulting colorless solid was collected by filtration to give **8a** (350 mg., 94%), m.p. 255° dec.; nmr δ (dimethylsulfoxide-d_6): 1.57 (3H, s, CH_3); 5.03 (2H, s, $CH_2N<$), 7.2-8.3 (8H, m, ArH).

Anal. Calcd. for $C_{19}H_{15}N_2O_5Na \cdot 0.5\ H_2O$: C, 59.53; H, 4.21; N, 7.31. Found: C, 59.17; H, 3.97; N, 7.03.

(b) Under the same conditions as above, **7b** (40 mg.) was saponified to afford **8b** (38 mg., 97%), m.p. 212° dec.; nmr δ (dimethylsulfoxide-d_6): 1.57 (3H, s, CH_3), 5.03 (2H, s, $CH_2N<$), 7.0-8.7 (8H, m, ArH), which was so hygroscopic that it was used without further purification in the following reaction.

(c) Under the same conditions as above, a mixture of **7a** and **7b** (400 mg.) was saponified to afford a mixture of **8a** and **8b** (390 mg., 99%).

2-Oxo-3-[4-(1-oxo-2-isoindolinyl)phenyl]butanamide (**9**).

(a) A mixture of **8a** (100 mg.) and acetic acid (5 ml.) was refluxed for 1.5 hours and the mixture was poured into ice water to give **9** (80 mg., 98%) as a solid, which was recrystallized from ethyl acetate to afford colorless needles, m.p. 210-212°; nmr δ (dimethylsulfoxide-d_6): 1.37 (3H, d, J = 7 Hz, CH_3), 4.76 (1H, q, J = 7 Hz, $>CH$), 5.03 (2H, s, $CH_2N<$), 7.1-8.2 (8H, m, ArH); ms: m/e 308 (M^+).

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.23; N, 9.09. Found: C, 69.75; H, 5.08; N, 8.90.

(b) A mixture of **8b** (10 mg.) and acetic acid (1 ml.) was refluxed for 2 hours and the mixture was poured into ice water to give **9** as colorless needles, which was identical with the above sample prepared by method (a).

(c) A mixture of **8a** and **8b** (1.15 g.) in acetic acid (20 ml.) was refluxed for 2 hours and the mixture was poured into ice water to give **9** (0.90 g., 95%) as a solid, which was recrystallized from ethyl acetate to afford colorless needles, which were identical with the above sample prepared by method (a).

Ethyl (E)- and (Z)-2-Cyano-3-methyl-3-[4-(1-oxo-2-isoindolinyl)-phenyl]oxiranecarboxylate (**11a**) and (**11b**).

To a mixture of ester **6a** (10.38 g.), ethanol (450 ml.), chloroform (50 ml.) and sodium phosphate dibasic dodecahydrate (5.37 g.) was added dropwise 28% hydrogen peroxide (4.1 ml.) with stirring at 70-80°. Stirring was continued for 1 hour at 70-80° and water (150 ml.) was added to the reaction mixture and then the solvent was distilled off until crystals began to appear. An additional water (500 ml.) was further added and the resulting precipitate collected was washed with water and dried to give a solid of a mixture of **11a** and **11b** (**11a**:**11b** = 2:1) (9.70 g., 89%), whose recrystallization from ethanol afforded (E)-isomer **11a** as colorless scales, m.p. 161-162°; ir ν max (potassium bromide): 2250 (C≡N), 1753 (C=O), 1728 (C=O) and 1672 cm^{-1} (C=O); nmr δ (deuteriochloroform): 1.40 (3H, t, J = 7 Hz, CH_2CH_3), 1.84 (3H, s, CH_3), 4.44 (2H, q, J = 7 Hz, CH_2CH_3), 4.88 (2H, (2H, s, CH_2N), 7.4-8.2 (8H, m, ArH).

Anal. Calcd. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.00; N, 7.73. Found: C, 69.28; H, 4.85; N, 7.60.

Evaporation of the mother liquor during the above recrystallization afforded a residue which was chromatographed on silica gel with chloroform to give a solid. Recrystallization from benzene-hexane afforded (Z)-isomer **11b** as colorless needles, m.p. 153-153.5°; ir ν max (potassium bromide): 2250 (C≡N), 1770 (C=O), 1736 (C=O) and 1676 cm^{-1} (C=O); nmr δ (deuteriochloroform): 1.04 (3H, t, J = 7 Hz, CH_2CH_3), 2.03 (3H, s, CH_3), 4.04 (2H, q, J = 7 Hz, CH_2CH_3), 4.86 (2H, s, $CH_2N<$), 7.3-8.1 (8H, m, ArH).

Anal. Calcd. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.00; N, 7.73. Found: C, 69.35; H, 5.17; N, 7.34.

Potassium (E)-2-Cyano-3-methyl-3-[4-(1-oxo-2-isoindolinyl)-phenyl]oxiranecarboxylate (**12a**).

To a solution of ester **11a** (160 mg.) in ethanol (10 ml.) was added 3% (w/w) ethanolic potassium hydroxide (1.17 ml.) and the mixture was allowed to stand overnight. Removal of the solvent followed by washing the resulting solid with ether-ethanol (1:1) yielded **12a** (157 mg., 95%) as a solid; ir ν max (potassium bromide): 2230 (C≡N), 1683 (C=O) and 1632 cm^{-1} (COO^-); nmr δ (dimethylsulfoxide-d_6): 1.73 (3H, s, CH_3), 5.07 (2H, s, CH_2N), 7.4-8.4 (8H, m, ArH), which was used without purification in the following reaction because of its hygroscopic character.

Potassium (Z)-2-Cyano-3-methyl-3-[4-(1-oxo-2-isoindolinyl)-phenyl]oxiranecarboxylate (**12b**).

Under the same conditions as above, **11b** (160 mg.) was saponified to give **12b** (143 mg., 87%); ir ν max (potassium bromide): 2240 (C≡N), 1680 (C=O) and 1648 cm^{-1} (COO^-); nmr δ (dimethylsulfoxide-d_6): 1.81 (3H, s, CH_3), 5.03 (2H, s, CH_2N), 7.3-8.0 (8H, m, ArH), which was also very hygroscopic.

2-Hydroxy-3-[4-(1-oxo-2-isoindolinyl)phenyl]-2-butenonitrile (**13**).

(a) To a solution of ester **11a** (320 mg.) in ethanol (20 ml.) was added 3% (w/w) ethanolic potassium hydroxide (2.33 ml.) and the mixture was allowed to stand overnight. After removal of the solvent, the resulting solid, which was identical with the above potassium salt **12a** in ir spectral comparison, was dissolved in water (20 ml.) and acidified with diluted hydrochloric acid. The mixture was extracted with ethyl acetate and the extract was washed with water, dried over magnesium sulfate and evaporated to give a solid of **13** (237 mg., 93%); ir ν max (potassium bromide): 2220 (C≡N) and 1650 (broad) cm^{-1}; nmr δ (dimethylsulfoxide-d_6): 2.90 and 2.21 [3H, (2.09:2.21 = 9:7), double s, CH_3], 5.01 (2H, s, CH_2N), 7.3-8.1 (8H, m, ArH).

(b) To a solution of ester **11b** (111 mg.) in ethanol (10 ml.) was added 3% (w/w) ethanolic potassium hydroxide (0.81 ml.) and the mixture was allowed to stand overnight. After removal of the solvent, the resulting solid, which was identical with the above potassium salt **12b** in ir spectral comparison, was dissolved in water (10 ml.), whose solution was acidified with diluted hydrochloric acid. The mixture was extracted with ethyl acetate and the extract was washed with water, dried over magnesium sulfate and evaporated to give **13** (81 mg., 91%) as a solid, ir ν max (potassium bromide): 2220 (C≡N), 1685 (shoulder) and 1656 cm^{-1}; nmr (dimethylsulfoxide-d_6): 2.09 and 2.21 [3H (2.09:2.21 = 1:5), double s, CH_3], 5.03 (2H, s, CH_2N), 7.3-8.2 (8H, m, ArH), which was used in the following reaction without purification because of its instability.

Methanolysis of 2-Hydroxy-3-[4-(1-oxo-2-isoindolinyl)phenyl]-2-butenonitrile (**13**).

(a) A solution of **13** (344 mg.) (obtained from **11a**) in methanol (40 ml.) was heated under reflux for 7 hours. After removal of the solvent, the residue was chromatographed on silica gel using chloroform as solvent to give methyl 2-[4-(1-oxo-2-isoindolinyl)phenyl]propionate (255 mg., 67% from **11a**) as colorless needles, m.p. 132-133° (from methanol) [lit. (5a), m.p. 124-126°]; ir ν max (potassium bromide): 1730 and 1670 cm^{-1} (C=O); nmr δ (deuteriochloroform): 1.53 (3H, d, J = 7 Hz, $CHCH_3$), 3.68 (3H, s, CO_2CH_3), 3.76 (1H, q, J = 7 Hz, $CHCH_3$), 4.83 (2H, s, CH_2N), 7.3-8.1 (8H, m, ArH).

(b) Treatment of **13** (184 mg.) (obtained from **11b**) with methanol under the same conditions as above afforded methyl 2-[4-oxo-2-isoindolinyl)phenyl]propionate (116 mg., 56% from **11b**).

2-Cyano-3-methyl-3-[4-(1-oxo-2-isoindolinyl)phenyl]oxirane (**13a**).

To a stirred solution of **2** (2.5 g.) and chloroacetonitrile (7.55 g.) in toluene (100 ml.) was added dropwise sodium tertiary amylate, prepared from sodium amide (5.46 g.) and tertiary amyl alcohol (10.57 g.) in toluene (200 ml.) at 50° for 3 hours, under ice-cooling and the stirring was continued for 1 hour. The reaction mixture was poured into water (50 ml.) and filtered to remove the inorganic substance. The toluene layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give an oil, which was triturated with *n*-hexane (50 ml.) to give crystals. This was passed through silica gel using chloroform as solvent to give a diastereomeric mixture of **13a** as crystals; ir ν max (potassium bromide): 2240 (CN) and 1680 cm^{-1} (C=O); nmr δ (deuteriochloroform): 1.80 and 1.97 (3H, each s, CH_3, ratio of isomers; 3:4), 3.37 and 3.60 (1H, each s, CH, ratio of isomers; 4:3), 4.85 (2H, s, CH_2N), 7.3-8.1 (8H, m, ArH).

Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.68; H, 4.72; N, 9.60.

Ethyl (E)- and (Z)-3-Methyl-3-[4-(1-oxo-2-isoindolinyl)phenyl]-oxiranecarboxylate (**14a**) and (**14b**).

To a stirred suspension of tetrahydrofuran (**11**), sodium amide (4 g.) and **2** (4.5 g.), ethyl chloroacetate (10 ml.) was added dropwise during 30 minutes at 10-20°, and the mixture was stirred for 16 hours. Stirring was continued for 1 hour at 40° and the resulting suspension was filtered. The organic layer was evaporated to give residue, which was chromatographed on silica gel using chloroform as an eluent. (E)-Stereoisomer **14a** (2.54 g., 42%) emerged first as colorless needles, m.p. 183-185° (from tetrahydrofuran-ethanol); ir ν max (potassium bromide): 1750 (C=O), 1710 (C=O) and 1680 cm^{-1} (C=O); nmr δ (deuteriochloroform): 1.34 (3H, t, J = 7 Hz, CH_2CH_3), 1.78 (3H, s, CH_3), 3.46 (1H, s, CH), 4.31 (2H, q, J = 7 Hz, CH_2CH_3), 4.83 (2H, s, $CH_2N<$), 7.3-8.1 (8H, m, ArH).

Anal. Calcd. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.23; H, 5.63; N, 4.20.

Elution of (Z)-stereoisomer **14b** gave colorless needles (1.06 g., 18%), m.p. 141-143° (from tetrahydrofuran-ethanol); ir ν max (potassium bromide): 1710 (C=O) and 1680 cm^{-1} (C=O); nmr δ (deuteriochloroform): 1.00 (3H, t, J = 7 Hz, CH_2CH_3), 1.77 (3H, s, CH_3), 3.70 (1H, s, CH), 3.98 (2H, q, J = 7 Hz, CH_2CH_3), 4.87 (2H, s, $CH_2N<$), 7.3-8.3 (8H, m, ArH).

Anal. Calcd. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.31; H, 5.62; N, 4.29.

Ethyl 2-Hydroxy-3-[4-(1-oxo-2-isoindolinyl)phenyl]-3-butenoate (**15**).

A mixture of **14a** and **14b** (**14a**:**14b** = 2.4:1) (400 mg.) and xylene (5 ml.) saturated with hydrogen chloride gas was refluxed for 30 minutes. After removal of the solvent, the residue was chromatographed on silica gel using chloroform as an eluent to give **15** (320 mg., 80%) as colorless scales, m.p. 115-117° (from benzene-carbon tetrachloride); ir ν max (potassium bromide): 1725 (C=O) and 1680 cm^{-1} (C=O); nmr δ (deuteriochloroform): 1.10 (3H, t, J = 7 Hz, CH_2CH_3), 3.60 (1H, broad s, OH), 4.18 (2H, q, J = 7 Hz, CH_2CH_3), 4.75 (2H, s, $CH_2N<$), 5.10 (1H, s, CH), 5.40 and 5.47 (1H each, double s, $>C=CH_2$), 7.3-8.0 (8H, m, ArH).

Anal. Calcd. for $C_{20}H_{19}NO_4 \cdot 0.2\ H_2O$: C, 70.44; H, 5.74; N, 4.11. Found: C, 70.57; H, 5.67; N, 3.94.

Ethyl 2-Acetoxy-3-[4-(1-oxo-2-isoindolinyl)phenyl]-3-butenoate (**16**).

A mixture of **14a** and **14b** (**14a**:**14b** = 2.4:1) (1.0 g.) and acetic acid (1 g.) was refluxed for 1 hour and the solvent was evaporated to give the butenoate **16** (942 mg., 84%) as colorless needles, m.p. 109-111° (from ether-petroleum ether); ir ν max (potassium bromide): 1725 (C=O) and 1680 cm^{-1} (C=O); nmr δ (deuteriochloroform): 1.17 (3H, t, J = 7 Hz, CH_2CH_3), 2.15 (3H, s, $COCH_3$), 4.12 (2H, q, J = 7 Hz, CH_2CH_3), 4.78 (2H, s, $CH_2N<$), 5.45 and 5.58 (1H, each, double s, $>C=CH_2$), 5.80 (1H, s, $>CH$), 7.3-7.9 (8H, m, ArH).

Anal. Calcd. for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.87; H, 5.55; N, 3.75.

Ethyl 2-Oxo-3-[4-(1-oxo-2-isoindolinyl)phenyl]butanoate (**17**).

(a) A mixture of **14a** (1 g.) and xylene (5 ml.) saturated with hydrogen chloride gas was refluxed for 24 hours with a bubbling of hydrogen chloride gas. After removal of the solvent, the residue was chromatographed on silica gel with chloroform to give **17** (700 mg., 70%) as colorless needles, m.p. 122-123° (from carbon tetrachloride); ir ν max (potassium bromide): 1720 (C=O) and 1675 cm^{-1} (C=O); nmr δ (deuteriochloroform): 1.26 (3H, t, J = 7 Hz, CH_2CH_3), 1.48 (3H, d, J = 6 Hz, $CHCH_3$), 4.27 (2H, q, J = 7 Hz, CH_2CH_3), 4.56 (1H, q, J = 6 Hz, $CHCH_3$), 4.91 (2H, s, $CH_2N<$), 7.2-8.0 (8H, m, ArH).

Anal. Calcd. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 70.93; H, 5.65; N, 4.15.

(b) A mixture of **14a** (50 mg.) and acetic acid (1 ml.) saturated with hydrogen chloride gas was refluxed for 6 hours with a bubbling of hydrogen chloride gas. After removal of the solvent, the residue was chromatographed on silica gel with chloroform to give a solid (37 mg., 74%), identical with the above sample of **17** on the comparison by ir and nmr spectra and tlc behaviors.

Potassium (E)-3-Methyl-3-[4-(1-oxo-2-isoindolinyl)phenyl]oxirane-carboxylate (**19a**).

To a solution of potassium hydroxide (180 mg.) in ethanol (50 ml.) was added **14a** (900 mg.) and the mixture was refluxed for 1 hour. Stirring was continued for 12 hours at room temperature and the solvent was concentrated to give **19a** (880 mg., 95%); ir ν max (potassium bromide): 1680 (C=O) and 1590 cm^{-1} (COO^-); nmr δ (dimethylsulfoxide-d_6): 1.64 (3H, s, CH_3), 2.98 (1H, s, CH), 5.03 (2H, s, $CH_2N<$), 7.3-8.4 (8H, m, ArH).

Potassium (Z)-3-Methyl-3-[4-(1-oxo-2-isoindolinyl)phenyl]oxirane-carboxylate (**19b**).

Under the same conditions as above, **14b** (600 mg.) was saponified to give **19b** (507 mg., 82%); ir ν max (potassium bromide): 1675 (C=O) and 1605 cm^{-1} (COO^-); nmr δ (dimethylsulfoxide-d_6): 1.60 (3H, s, CH_3), 3.27 (1H, s, $>CH$), 5.02 (2H, s, $CH_2N<$), 7.3-8.3 (8H, m, ArH).

2-[4-(1-Oxo-2-isoindolinyl)phenyl]propanol (**18**).

(a) A mixture of **14a** and **14b** (**14a**:**14b** = 2.4:1) (40 mg.), concentrated hydrochloric acid (1 ml.) and acetic acid (3 ml.) was refluxed for 6 hours and the solvent was evaporated off. To the residue was added 10% (w/w) aqueous sodium hydroxide solution (5 ml.) and ethanol (5 ml.) and the resulting mixture was extracted with chloroform. The chloroform layer was dried over magnesium sulfate and evaporated to give **18** (13 mg., 43%) as colorless needles, m.p. 161-165° (from ethanol); ir ν max (potassium bromide): 1680 cm^{-1} (C=O); nmr δ (deuteriochloroform): 1.40 (3H, d, J = 7 Hz, $CHCH_3$), 3.58 (1H, q, J = 7 Hz, $CHCH_3$), 4.78 (2H, s, $CH_2N<$), 7.1-8.0 (8H, m, ArH), 9.63 (1H, s, CHO).

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.70; H, 5.77; N, 5.49.

The above alkaline solution was acidified with diluted hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and evaporated to give a solid (15 mg., 41%), which was identical with the authentic sample of **10** described above.

(b) A mixture of **19a** (100 mg.) and diluted hydrochloric acid (5 ml.) was heated at 50° for 30 minutes. The resulting precipitate was collected and recrystallized from ethanol to afford colorless needles (69 mg., 90%), m.p. 161-165°, identical with the above sample of **18** on the comparisons by ir and nmr spectra and tlc behaviors.

(c) Under the same conditions as the above method (b), **19b** (50 mg.) gave colorless needles (33 mg., 86%), m.p. 161-165° (from ethanol), which was identical with the above sample of **18** on the comparisons by ir and nmr spectra and tlc behaviors.

2-Oxo-3-[4-(1-oxo-2-isoindolinyl)phenyl]butanoic Acid (**10**).

(a) A mixture of **9** (300 mg.) and 10% (w/w) aqueous sodium hydroxide solution (10 ml.) was refluxed for 1 hour and the alkaline solution was washed with chloroform, followed by acidification with diluted hydrochloric acid. The mixture was extracted with chloroform and the extract was washed with water, dried over sodium sulfate and evaporated. The residue was recrystallized from ethyl acetate to afford **10** (230 mg., 76%) as colorless scales, m.p. 216-219°; nmr δ (dimethylsulfoxide-d_6-tetradeuteriomethanol): 1.47 (3H, d, J = 7 Hz, $CHCH_3$), 4.55 (1H, q, J = 7 Hz, $CHCH_3$), 4.92 (2H, s, $CH_2N<$), 7.2-8.1 (8H, m, ArH); ms: m/e 309 (M^+).

Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; H, 4.53. Found: C, 69.70; H, 4.90; N, 4.43.

(b) A mixture of **14a** (50 mg.) and acetic acid (2 ml.) saturated with hydrogen chloride gas was refluxed for 24 hours with a bubbling of hydrogen chloride gas and the solvent was evaporated to give a residue, identical with the sample of **17**, to which was added 10% (w/w) aqueous sodium hydroxide solution (5 ml.) and ethanol (5 ml.) and the mixture was heated at 70° for 10 minutes. The alkaline solution was washed with chloroform, acidified with diluted hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and evaporated to give **10** (20 mg., 50%) as colorless scales, m.p. 216-219° (from ethyl acetate), which was identical with the above sample prepared by method (a).

(c) A mixture of **14a** (100 mg.) and xylene (2 ml.) saturated with hydrogen chloride was refluxed for 24 hours with a bubbling of hydrogen chloride and the solvent was evaporated to give a residue, identical with the sample of **17**, to which was added 10% (w/w) aqueous sodium hydroxide solution (5 ml.) and ethanol (5 ml.) and the mixture was heated at 70° for 10 minutes. The alkaline solution was washed with chloroform, acidified with diluted hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and evaporated to give **10** (53 mg., 58%), which was identical with the above sample prepared by method (a).

2-[4-(1-Oxo-2-isoindolinyl)phenyl]propanoic Acid (**1**).

(a) A suspension of **9** (10 g.) in 10% (w/w) aqueous sodium hydroxide solution (100 ml.) was heated at 100° for 40 minutes. After cooling, 28% hydrogen peroxide (10 ml.) was added to the above alkaline solution and the mixture was allowed to stand overnight. The aqueous solution was washed with chloroform and acidified with concentrated hydrochloric acid. The resulting precipitate was collected and recrystallized from ethanol to afford **1** (6.5 g., 71%) as colorless scales, m.p. 213-214° [lit. (5a) m.p. 213-214°]; ir ν max (potassium bromide): 1680 cm^{-1} (C=O); nmr δ (dimethylsulfoxide-d_6): 1.37 (3H, d, J = 7 Hz, $CHCH_3$),

3.68 (1H, q, J = 7 Hz, C*H*Cl_3), 5.00 (2H, s, $CH_2N<$), 7.2-8.0 (8H, m, ArH); ms: m/e 281 (M^+).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.13; H, 5.39; N, 4.94.

(b) To a mixture of **10** (300 mg.) in 10% (w/w) aqueous sodium hydroxide solution (5 ml.) was added 30% hydrogen peroxide (1 ml.) with stirring at 0° and the mixture was allowed to stand at room temperature overnight. The alkaline solution was washed with chloroform, acidified with diluted hydrochloric acid and extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated to leave a solid, whose recrystallization from ethanol afforded colorless scales (250 mg., 92%), m.p. 213-214°, showing ir and nmr spectra consistent with the above sample of **1**.

(c) To a suspension of **13** (227 mg.) (obtained from **11a**) in benzene (40 ml.) was added 20% aqueous sodium hydroxide solution (10 ml.) with stirring at 80-90° and stirring was continued at 80-90° for 2 hours. After cooling, the separated organic layer was washed with 10% aqueous sodium hydroxide solution (5 ml. x 2). The combined alkaline solution was acidified with concentrated hydrochloric acid and the resulting precipitate was collected by filtration, washed with water, dried and chromatographed on silica gel using chloroform-ethanol (100:5) as solvent to give **1** (117 mg., 47% from **11a**), m.p. 213-214° (from ethanol), showing ir and nmr spectra consistent with the above sample of **1**.

(d) Under the same conditions as the above method (c), **13** (55 mg.) (obtained from **11b**) afforded **1** (25 mg., 43% from **11b**).

(e) To a solution of **11a** and **11b** (2.57 g.) (**11a**:**11b** = 4:3) in ethanol (100 ml.) was added a solution of potassium hydroxide (0.56 g.) in ethanol (10 ml.) and the mixture was allowed to stand overnight. After removal of the solvent, the residue was dissolved into water (100 ml.) and acidified with diluted hydrochloric acid. The mixture was extracted with ethyl acetate and the extract was washed with water dried over magnesium sulfate and evaporated. To a suspension of the resulting solid in benzene (100 ml.) was added 20% aqueous sodium hydroxide solution (10 ml.) with stirring at 80-90° and stirring was continued for 2 hours at 80-90°. After cooling, the separated organic layer was washed with 10% aqueous sodium hydroxide solution (10 ml. x 2). The combined alkaline solution was washed with ethyl acetate several times and acidified with concentrated hydrochloric acid. The resulting precipitate was collected and recrystallized from ethanol to afford colorless scales (0.95 g., 47.5% from **11a** and **11b**), m.p. 213-214°, showing ir and nmr spectra consistent with the above sample of **1**.

Cinchonidine (+)- and (-)-2-[4-(1-Oxo-2-isoindolinyl)phenyl]propanoate.

A mixture of (±)-**1** (2.97 g.) and cinchonidine (3.11 g.) was dissolved in ethanol (70 ml.) by warming and the mixture was allowed to stand overnight. The resulting crystals were collected by filtration and recrystallized from ethanol to afford cinchonidine salt of (+)-**1** (2.45 g., 81%) as colorless scales, m.p. 205-207°.

Anal. Calcd. for $C_{36}H_{37}N_3O_4$: C, 75.10; H, 6.48; N, 7.30. Found: C, 75.28; H, 6.70; N, 7.01.

The ethanolic mother liquor during recrystallization was evaporated to give a solid, which was recrystallized from isopropanol to afford cinchonidine salt of (-)-**1** (1.2 g., 39%) as colorless scales, m.p. 176-177°.

Anal. Calcd. for $C_{36}H_{37}N_3O_4 \cdot H_2O$: C, 72.82; H, 6.62; N, 7.08. Found: C, 73.19; H, 6.65; N, 6.94.

(+)-2-[4-(1-Oxo-2-isoindolinyl)phenyl]propanoic Acid.

A suspension of cinchonidine salt of (+)-**1** (2.05 g.) in ethyl acetate (100 ml.) was washed with diluted hydrochloric acid and water. The organic layer was dried over sodium sulfate and evaporated to give a solid, which was recrystallized from isopropanol to afford (+)-**1** (0.78 g., 78%) as colorless scales, m.p. 205-207°, showing the nmr spectrum consistent with racemic **1**: $[\alpha]_D^{20}$ = +48° (c = 0.05, dimethyl sulfoxide, l = 0.1 dm).

Anal. Calcd. for $C_{17}H_{15}NO_3 \cdot 0.25\ H_2O$: C, 71.44; H, 5.47; N, 4.90. Found: C, 71.81; H, 5.30; N, 4.76.

(-)-2-[4-(1-Oxo-2-isoindolinyl)phenyl]propanoic Acid.

Under the same conditions as above, cinchonidine salt of (-)-**1** (1.2 g.) afforded (-)-**1** (0.5 g., 85%) as colorless scales, m.p. 205-207° (from 2-propanol), showing the nmr spectrum consistent with racemic **1**: $[\alpha]_D^{20}$ = -48° (c = 0.05, dimethylsulfoxide, l = 0.1 dm).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.44; H, 5.36; N, 4.68.

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