Studies on the Synthesis of Analgesics. Part 51 (1). Synthesis of 4-(1-Oxo-2-isoindolinyl)phenyl Derivatives. [Studies on the Syntheses of Heterocyclic Compounds. Part 779 (2)]

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In order to examine their effect on carrageenin-induced edema in rats, 4-(1-oxo-2-isoindolinyl)-phenyl derivatives were synthesized. 2-Hydroxy-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyramide was found to be more effective than phenylbutazone.

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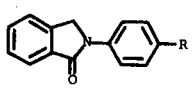
It is well known that a number of phenylacetic and phenylpropionic acid derivatives show analgesic and anti-inflammatory activities (4). We have also investigated the synthesis of these types of compounds. In a previous paper (1) we reported three new synthetic routes to 2-[4-(1-oxo-2-isoindolinyl)phenyl]propionic acid (**1**) (5), which shows analgesic and antiinflammatory activities. As a continuation of this study, we have examined the synthesis of derivtives with several substituents on the 4-position of the aniline part of the title compound in order to obtain new antiinflammatory and analgesic substances. Here we report the synthesis of several compounds shown in Scheme 1 from 2-oxo-3-[4-(1-oxo-2-isoindolinyl)phenyl]-butyramide (**2**), which is a key intermediate to **1** (1).

Scheme 1



(1) R=-CH(CH$_3$)COOH

(2) R=-CH(CH$_3$)COCONH$_2$

(3a and 3b) R=-CH(CH$_3$)CH(OH)CONH$_2$

(4) R=-CH(CH$_3$)CH(OCOCH$_3$)CONH$_2$

(5) R=-CH(CH$_3$)CH(OCOCH$_3$)CONHCOCH$_3$

(6) R=-CH(CH$_3$)CH(OCOCH$_3$)CN

(7) R=-CH(CH$_3$)CH(OTs)CN

(8) R=-CH(CH$_3$)CH(OTs)CONH$_2$

(9) R=-CH(CH$_3$)COCOOH

(10) R=-CH(CH$_3$)COCOOEt

(11) R=-CH(CH$_3$)C(=NOH)CONH$_2$

(12) R=-CH(CH$_3$)C(=NOH)COOEt

(13) R=-CH(CH$_3$)C(=NOH)COOH

(14) R=-CH(CH$_3$)CN

(15) R=-C(CH$_3$)=C(OCOCH$_3$)CONH$_2$

Catalytic hydrogenation of the starting material **2** on platinum oxide gave a distereoisomeric mixture of 2-hydroxy-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyramide (**3a** and **3b**) in a ratio of 2 to 1 (6), which was separated by column chromatography on silica gel. The reduction of **2** with sodium borohydride provided a mixutre of **3a** and **3b** in a ratio of 7 to 1.

Treatment of **3a** with acetic anhydride afforded the acetylated products, 2-acetoxy-3-[4-(1-oxo-2-isoindolinyl)-phenyl]butyramide (**4**) [ms: m/e 352 (M$^+$)] and its *N*-acetyl derivative **5** [ms: m/e 392 (M$^+$)], in addition to 2-acetoxy-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyronitrile (**6**) [ms: m/e 334 (M$^+$)], which is a dehydration product of **4**. However, the reaction of **3a** with acetic anhydride in pyridine at room temperature gave only the *O*-acetyl derivative **4**, which was converted into the *N,O*-diacetyl compound **5** by heating with acetic anhydride.

On the other hand, treatment of **3a** with *p*-toluene-sulfonyl chloride in pyridine afforded 2-tosyloxy-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyronitrile (**7**) by tosylation and dehydration, together with 2-tosyloxy-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyramide (**8**), which is the normal reaction product. The former compound **7** was transformed into the amide **8** by treatment with hydrogen peroxide in the presence of sodium phosphate.

Oximination of the starting compound **2** and of the corresponding carboxylic ester **10** was also examined. Heating **2** with hydroxylamine hydrochloride in ethanol in the presence of pyridine gave the expected oxime **11** and the same treatment of the ester **10** afforded the second oxime **12**, whose hydrolysis with sodium hydroxide provided the carboxylic acid **13** havine an oxime group. Treatment of the keto acid (**9**) with hydroxylamine hydrochloride in ethanol and pyridine caused a fragmentation reaction to form 2-[4-(1-oxo-2-isoindolinyl)phenyl]propiononitrile (**14**), by decarboxylation and dehydration, as shown in Scheme 2. A similar type of reaction has been reported by Dieckmann (7) in the conversion of α-hydroxyimino-succinic acid into cyanoacetic acid.

Acetylation of the starting compound **2** with acetic anhydride in pyridine gave the enol acetate **15** [ms: m/e 350 (M$^+$)] which showed acetoxyl methyl and olefinic methyl resonances at 2.00 and 2.50 ppm, respectively, in the nmr spectrum.

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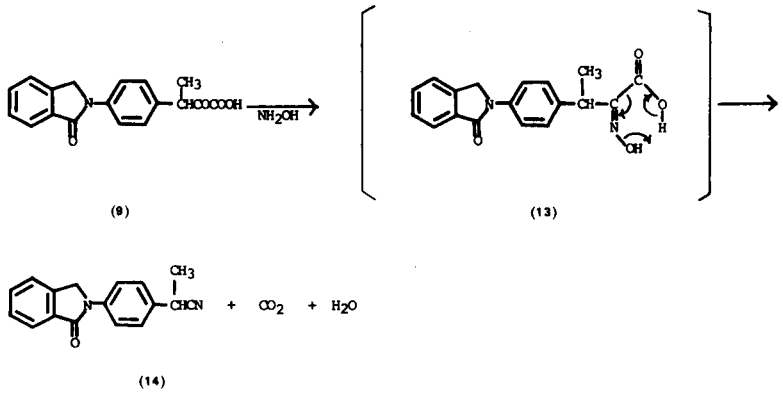
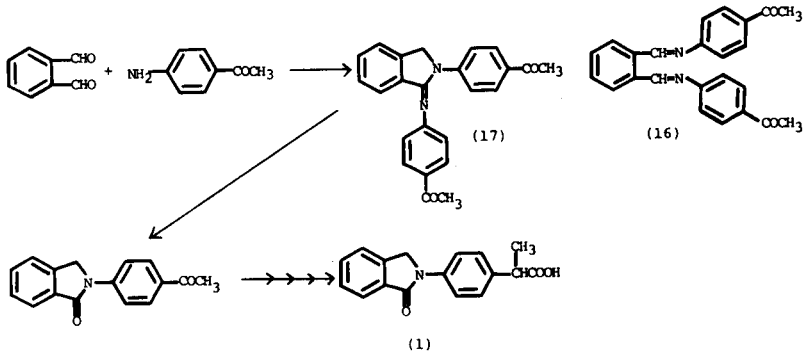
Scheme 2



Scheme 3



The examination of inhibitory effect on carrageenin paw edema by the compounds prepared in this paper revealed that 2-hydroxy-3-[4-1-oxo-2-isoindolinyl)phenyl]-butyramides (**3a** and **3b**) were more effective than phenylbutazone.

Previously, we have reported syntheses of 2-[4-(1-xoxo-2-isoindolinyl)phenyl]propionic acid (**1**) as shown in Scheme 3 (1), in which the condensation product of phthalaldehyde and 4-aminoacetophenone was assigned the structure **16**. However, on careful analysis of the nmr spectrum of this condensation product, which showed methylene proton resonance (singlet, 5.03 ppm) in addition to two methyl resonances at 2.60 and 2.67 and aromatic proton resonance at 6.7-8.3, we wish to revise this structure and propose formula **17**. The benzylidene structure **16**, in which the methine proton resonance would be expected at 7 ppm (8), is thus ruled out.

The new compounds **3a** and **3b**, whose syntheses have been described above, show strong antiinflammatory activity and we are now investigating possible analgesic and antipyretic activities of the same compounds.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were measured on a Hitachi-215 spectrophotometer and nmr spectra on a JEOL-PMX-60 spectrometer, using tetramethylsilane as internal reference.

2-Hydroxy-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyramide (**3a**) and (**3b**).

a.

A suspension of 2-oxo-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyramide (**2**) (3.08 g.) and platinum oxide (0.3 g.) in methanol (50 ml.) was stirred for 5 hours at room temperature, under hydrogen (1 atmosphere). After filtration to remove the catalyst, evaporation of the solvent gave a white solid (2.97 g., 96%), which was shown to be a mixture of **3a** and **3b** (2:1) by nmr analysis. This product was subjected to column chromatography on silica gel (100 g.). The eluate with chloroform-methanol (50:1 v/v) was evaporated and the residue recrystallized from methanol to afford **3b** as colorless prisms, m.p. 199-201°; ir max (potassium bromide): 3350 (OH) and 1670 cm^{-1} (C=O); nmr (DMSO-d_6): δ 1.26 (3H, d, J = 7 Hz, $CHCH_3$), 3.26-3.70 (1H, m, $CHCH_3$), 4.23 (1H, q, J = 3 and 6 Hz, $CHOH$), 4.97 (2H, s, CH_2N), 5.20 (1H, d, J = 6 Hz, $CHOH$), 6.53-7.30 (2H, br s, NH_2), and 7.46-8.03 (8H, m, ArH); ms: m/e 310 (M^+).

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.36; H, 6.06; N, 8.80.

The eluate with chloroform-methanol (1:1v/v) was evaporated and the residue recrystallised from methanol to afford **3a** as colorless needles, m.p. 206-207°; ir max (potassium bromide): 3420 (OH) and 1650 (C=O); nmr (DMSO-d_6): δ 1.40 (3H, d, J = 7 Hz, $CHCH_3$), 3.00-3.50 (1H, m, $CHCH_3$), 4.12 (1H, q, J = 4 and 5 Hz, $CHOH$), 4.90 (2H, s, CH_2N), 5.23 (1H, d, J = 5 Hz, $CHOH$), 6.53-6.85 (2H, br s, NH_2), and 7.20-7.90 (8H, m, ArH); ms: m/e 310 (M^+).

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.53; H, 5.75; N, 8.78.

b.

To a suspension of 2-oxo-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyramide

(**2**) (3 g.) in methanol (50 ml.), sodium borohydride (0.25 g.) was added slowly with stirring and cooling with ice. The mixture was further stirred for 3 hours at room temperature. After addition of acetone the resulting mixture was evaporated to give a residue, to which water was added, giving a mixture of **3a** and **3b** (7:1 from nmr analysis as a white solid (33 g., 99%).

2-Acetoxy-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyramide (**4**).

A mixture of 2-hydroxy-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyramide (**3a**) (4 g.), acetic anhydride (2.5 ml.) and pyridine (20 ml.) was set aside for 15 hours at room temperature and then poured into water. The precipitated solid was collected by filtration and was washed with water. After drying, recrystallization from methanol gave **4** (3.5 g., 77%) as colorless prisms, m.p. 220-222°; ir max (potassium bromide): 1735 (C=O) and 1660 cm^{-1} (C=O); nmr (acetic acid-d_4: deuteriochloroform): δ 1.33 (3H, d, J = 7 Hz, $CHCH_3$), 2.08 (3H, s, $OCOCH_3$), 3.20-3.28 (1H, m, $CHCH_3$), 4.80 (2H, s, CH_2N), 5.28 (1H, d, J = 6 Hz, $CHOCOCH_3$), and 7.10-7.90 (10H, m, ArH and NH_2); ms: m/e 352 (M^+).

Anal. Calcd. for $C_{20}H_{20}N_2O_4 \cdot 0.25H_2O$: C, 67.30; H, 5.78; N, 7.84. Found: C, 67.42; H, 5.95; N, 7.74.

2-Acetoxy-*N*-acetyl-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyramide (**5**).

A mixture of 2-acetoxy-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyramide (**4**) (4 g.) and acetic anhydride (20 ml.) was refluxed for 2 hours. After cooling, followed by addition of water (150 ml.), the resulting mixture was extracted with chloroform. The chloroform layer was washed with water, dried over magnesium sulfate, and evaporated to give a residue, which was recrystallized from ethanol to afford **5** (3.2 g., 72%) as colorless needles, m.p. 100-102°; ir max (potassium bromide): 1740 (C=O), 1720 (C=O), and 1690 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.35 (3H, d, J = 7 Hz, $CHCH_3$), 2.10 (3H, s, $OCOCH_3$), 2.36 (3H, s, $NHCOCH_3$), 3.26-3.76 (1H, m, $CHCH_3$), 4.75 (2H, s, CH_2N), 5.35 (1H, d, J = 6 Hz, $CHOCOCH_3$), and 7.20-8.00 (9H, m, ArH and NH); ms: m/e 394 (M^+).

Anal. Calcd. for $C_{22}H_{22}N_2O_5 \cdot 0.5H_2O$: C, 65.50; H, 5.75; N, 6.94. Found: C, 65.16; H, 5.76; N, 6.56.

2-Acetoxy-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyronitrile (**6**).

A mixture of 2-hydroxy-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyramide (**3a**) (2 g.) and acetic anhydride (40 ml.) was refluxed for 20 minutes. After cooling, followed by addition of water (50 ml.), the resulting mixture was extracted with chloroform. The chloroform extract was washed with water, dried over magnesium sulfate, and evaporated. The residue was subjected to column chromatography on silica gel (50 g.). Elution with chloroform, followed by recrystallization from isopropanol afforded **6** (1 g., 47%) as colorless needles, m.p. 132-133°; ir max (potassium bromide): 1740 (C=O) and 1680 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.53 (3H, d, J = 7 Hz, $CHCH_3$), 2.08 (3H, s, $OCOCH_3$), 3.20-3.40 (1H, m, $CHCH_3$), 4.80 (2H, s, CH_2N), 5.36 (1H, d, J = 6 Hz, $CHOCOCH_3$), and 7.20-7.93 (8H, m, ArH); ms: m/e 334 (M^+).

Anal. Calcd. for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 72.09; H, 5.57; N, 8.48.

The residue from the above mother liquor was recrystallized from methanol to give **5** (0.4 g., 16%).

Further elution with methanol, followed by recrystallization from methanol yielded **4** (0.6 g., 26%) as colorless needles, m.p. 220-222°.

3-[4-(1-Oxo-2-isoindolinyl)phenyl]-2-tosyloxybutyronitrile (**7**) and 3-[4-(1-Oxo-2-isoindolinyl)phenyl]-2-tosyloxybutyramide (**8**).

A mixture of 2-hydroxy-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyramide (**3a**) (5 g.), *p*-toluenesulfonyl chloride (3.5 g.) and pyridine (30 ml.) was set aside for 16 hours at room temperature. After addition of water (50 ml.), the resulting mixture was extracted with chloroform. The extract was washed with water, dried over magnesium sulfate and evaporated to give a residue, which was subjected to column chromatography on silica gel (100 g.). Elution with chloroform, followed by recrystallization from methanol afforded **7** (3.6 g., 50%) as colorless needles, m.p. 205-206°; ir max (potassium bromide): 1660 cm^{-1}, (C=O); nmr (acetic acid-d_4: deuteriochloroform): δ 1.25 (3H, d, J = 7 Hz, $CHCH_3$), 2.16 (3H, s, Ph-CH_3), 2.91-3.30 (1H, m, $CHCH_3$), 4.68 (2H, s, CH_2N), 4.97 (1H, d, J = 6 Hz, CHCN), and 6.97-7.87 (12H, m, ArH); ms: m/e 446 (M^+).

Anal. Calcd. for $C_{25}H_{22}N_2O_4S$: C, 67.24; H, 4.96; N, 6.27. Found: C, 67.44; H, 4.89; N, 6.17.

Further elution with methanol, followed by recrystallization from methanol yielded **8** (1.8 g., 24%) as colorless prisms, m.p. 202-204°; ir max (potassium bromide): 3400 (OH), 3150 (NH), and 1660 cm^{-1} (C=O); nmr (DMSO-d_6): δ 1.16 (3H, d, J = 7 Hz, $CHCH_3$), 2.33 (3H, s, Ph-CH_3), 3.00-3.41 (1H, m, $CHCH_3$), 4.70 (1H, d, J = 8 Hz, CHOTs), 5.00 (2H, s, CH_2N), and 7.00-7.80 (14H, m, ArH and NH_2); ms: m/e 464 (M^+).

Anal. Calcd. for $C_{25}H_{24}N_2O_5S$: C, 64.63; H, 5.21; N, 6.03; S, 6.90. Found: C, 64.82; H, 5.11; N, 5.96; S, 7.18.

Conversion of **7** into **8**.

A mixture of 3-[4-(1-oxo-2-isoindolinyl)phenyl]-2-tosyloxybutyronitrile (**7**) (2 g.), sodium phosphate twelve hydrate (0.3 g.), 28% hydrogen peroxide (1.5 ml.) and ethanol (3 ml.) was heated for 3 hours at 70°. After evaporation of the solvent, water (20 ml.) was added to the residue. The resulting mixture was extracted with chloroform and the extract was washed with water and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was recrystallized from methanol to afford **8** (1.5 g., 72%) as colorless needles, m.p. 202-204°.

2-Oxo-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyramide Oxime (**11**).

A mixture of 2-oxo-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyramide (**3a**) (1 g.), hydroxylamine hydrochloride (1 g.), pyridine (5 ml.) and ethanol (5 ml.) was refluxed for 3 hours. After evaporation of pyridine and ethanol, water (20 ml.) was added to the residue and the precipitated solid was filtered, washed with water, dried, and recrystallized from methanol to give **11** (1.54 g., 51%) as colorless needles, m.p. 225-227°; ir max (potassium bromide): 1675 (C=O) and 1650 cm^{-1} (C=O); nmr (DMSO-d_6): δ 1.54 (3H, d, J = 7 Hz, $CHCH_3$), 4.58 (1H, q, J = 7 Hz, $CHCH_3$), 4.98 (2H, s, CH_2N), 7.0-8.0 (10H, m, $CONH_2$ and ArH), and 11.52 (1H, s, NOH).

Anal. Calcd. for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 67.03; H, 5.15; N, 13.13.

Ethyl 2-Oxo-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyrate Oxime (**12**).

A mixture of ethyl 2-oxo-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyrate (**10**) (1 g.), hydroxylamine hydrochloride (1 g.), pyridine (5 ml.) and ethanol (5 ml.) was refluxed for 3 hours. The same work-up as above, followed by recrystallization from methanol yielded **12** (0.71 g., 67%) as colorless scales, m.p. 194-197°; ir max (potassium bromide): 1720 (C=O) and 1670 cm^{-1} (C=O); nmr (DMSO-d_6): δ 1.18 (3H, t, J = 7 Hz, CH_2CH_3), 1.52 (3H, d, J = 7 Hz, $CHCH_3$), 4.13 (2H, q, J = 7 Hz, CH_2CH_3), 4.68 (1H, q, J = 7 Hz, $CHCH_3$), 4.98 (2H, s, CH_2N), 7.1-8.0 (8H, m, ArH), and 12.46 (1H, s, NOH).

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.39; H, 5.68; N, 7.82.

2-Oxo-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyric Acid Oxime (**13**).

A mixture of ethyl 2-oxo-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyrate oxime (**12**) (0.71 g.), 10% aqueous sodium hydroxide (5 ml.) and ethanol (5 ml.) was heated for 1.5 hour at 80-85°. After evaporation of the solvent, the residual solution was acidified with 10% hydrochloric acid with cooling. The precipitate was filtered, washed with water, dried, and recrystallized from methanol-chloroform-ligroin to give **13** (0.35 g., 54%) as colorless granules, m.p. 172-174° dec.; ir max (potassium bromide): 1690 (C=O) and 1670 cm^{-1} (C=O); nmr (DMSO-d_6): δ 1.54 (3H, d, J = 7 Hz, $CHCH_3$), 4.64 (1H, q, J = 7 Hz, $CHCH_3$), 5.00 (2H, s, CH_2N), 7.1-8.0 (8H, m, ArH), and 12.50 (2H, br s, NOH and COOH).

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.39; H, 4.87; N, 8.43.

2-[4-(1-Oxo-2-isoindolinyl)phenyl]propiononitrile (**14**).

A mixture of 2-oxo-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyric acid (**9**) (1) (0.65 g.), hydroxylamine hydrochloride (0.65 g.), pyridine (3.25 ml.) and

ethanol (3.25 ml.) was refluxed for 2 hours. After evaporation of the solvent, water was added to the residue. The precipitated solid was washed with water, dried and then subjected to silica gel column chromatography. Elution with chloroform followed by recrystallization from ethanol yielded **14** (0.35 g., 64%) as colorless scales, m.p. 206-207° (lit. (9), m.p. 192-194°); ir max (potassium bromide): 2230 (CN) and 1680 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.68 (3H, d, J = 7 Hz, $CHCH_3$), 3.93 (1H, q, J = 7 Hz, $CHCH_3$), 4.87 (2H, s, CH_2N), and 7.2-8.1 (8H, m, ArH).

2-Acetoxy-3-[4-(1-oxo-2-isoindolinyl)phenyl]-2-butenamide (**15**).

To a suspension of 2-oxo-3-[4-(1-oxo-2-isoindolinyl)phenyl]butyramide (**2**) (1 g.) in pyridine (30 ml.) was added acetic anhydride (1 ml.) and the mixture was set aside for 5 days at room temperature. Crystals (0.55 g., 48%) which formed were collected by filtration and recrystallized from acetic acid giving colorless needles, m.p. 214-216°; nmr (acetic acid-d_4: deuteriochloroform): δ 2.00 (3H, s, $OCOCH_3$), 2.50 (3H, s, CH_3), 5.02 (2H, s, CH_2N), and 7.4-8.2 (8H, m, ArH); ms: m/e 350 (M^+).

Anal. Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.15; H, 5.22; N, 7.69.

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