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A Convenient Preparation of 8-Ethyl-4,9-dihydro-3H-pyrano[3,4-b]indole-1-one, Key Intermediate of the Antiinflammatory Agent Etodolac

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A CONVENIENT PREPARATION OF 8-ETHYL-4,9-DIHYDRO-3H-PYRANO[3,4-b] INDOLE-1-ONE, KEY INTERMEDIATE OF THE ANTIINFLAMMATORY AGENT ETODOLAC

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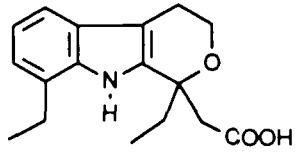
Abstract: A facile synthesis of 8-ethyl-4,9-dihydro-3H-pyrano [3,4-b]indole-1-one **5** is described which features the condensation of hydrazines with 2-oxo-5-hydroxypentanoic acid, followed by Fischer cyclization of these adducts.

1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid **1** (Etodolac) is an important nonsteroidal analgesic and antiinflammatory drug[1,2].



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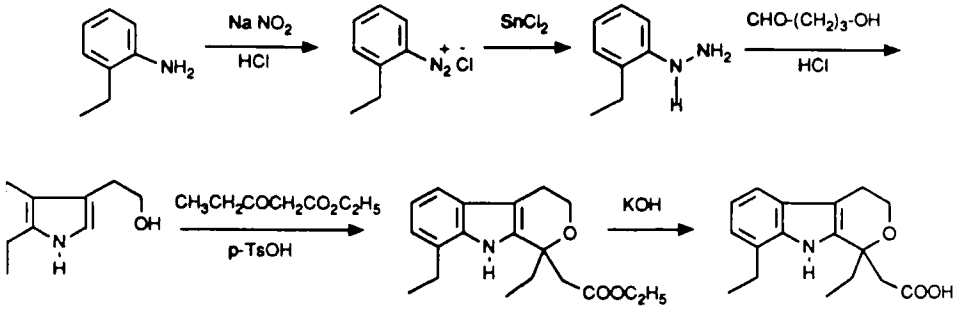
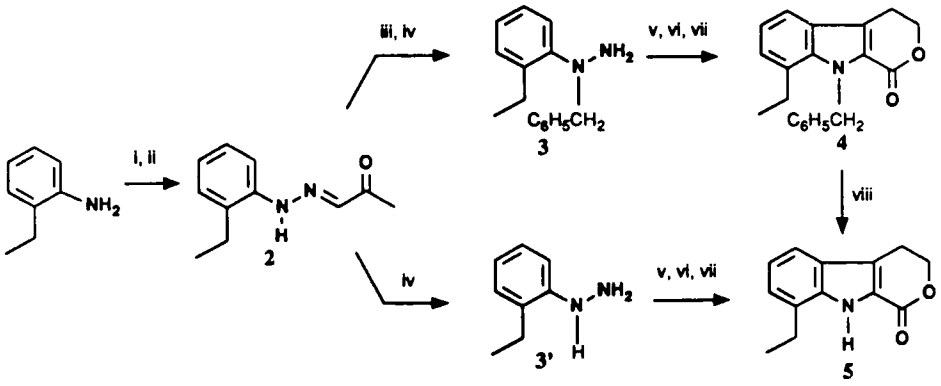
Etodolac and similar derivatives have been synthetized in the literature *via* the Fischer indolization between substituted phenylhydrazines and appropiate carbonyl compounds[3-5]. The key phenylhydrazines have commonly been prepared by reduction of the diazonium salts with *excess* of $SnCl_2$ in the presence of hydrochloric acid, which makes this method unatractive at a large scale (Scheme 1).



Scheme 1

We[6] and others[7] have recently described an operationally simple synthesis of N-alkyl-N-arylhydrazines. We envisioned, for the synthesis of the key intermediate **5**, condensation of phenylhydrazine **3** and the readily available 2-oxo-5-hydroxypentanoic acid to the corresponding hydrazone, followed by Fischer indolization to **4**. Lactone **4** could then be converted to **5** which can ultimately be decarboxylated to the tryptophol (Scheme 2). For the protection of the hydrazine, we chose the N-benzyl group, which had been established to be very stable and also easily removable at the end of the process[8-10]. After establishing the sequence, we also made **5** starting directly from phenylhydrazine **3'** also available by hydrazinolysis of **2**, followed by condensation with 2-oxo-5-hydroxypentanoic acid and cyclization with hydrogen chloride under identical conditions.

As schown in scheme 2, synthesis of the requisite N-benzyl-N-(2-ethylphenyl)hydrazine **3** was readily achieved in excellent yield by reaction of the hydrazone **2** with benzyl bromide followed by hydrazinolysis with 98% hydrazine hydrate[6]. Reaction of **3** with 2-oxo-5-hydroxypentanoic acid[11] in dimethylformamide[12]in the presence of hydrochloric acid produced the corresponding hydrazone, which was used without further purification. Fischer cyclization of this intermediate in $HCl_{(g)}$/DMF, followed by extraction, evaporation and flash chromatography, afforded lactone **4**. Deprotection of the lactone **4** was accomplished at room temperature with aluminium trichloride in



i) Na NO_2/HCl, 0°C ii) CH_3COCH_2COOH iii) 50% NaOH, TEBA, CH_2Cl_2, $C_6H_5CH_2Br$ iv) 98% NH_2NH_2/HCl, 100°C v) "$HOCH_2CH_2CH_2COCOOH$" vi) aq. HCl vii) $HCl_{(g)}$ viii) $AlCl_3/CH_3OC_6H_5$ room temp., 1.5 h.

Scheme 2

anisole[10] for 1.5 h to give the desired **5** in 33% overall yield from the starting 2-ethylaniline.

On the other hand, reaction of the hydrazone **2** with 98% hydrazine hydrate led to **3'**, which was condensed with 2-oxo-5-hydroxypentanoic acid under analogous conditions. Fischer cyclization of this hydrazone in $HCl_{(g)}$/DMF gave lactone **5** in 38% overall yield from 2-ethylaniline.

In conclusion, mild reaction conditions, simple work-up and moderate yields of the key intermediate **5**, make this method a useful contribution to etodolac synthesis.

EXPERIMENTAL SECTION

N-Benzyl-N-(2-ethylphenyl)hydrazine 3

Benzyl bromide (3.8 mL, 5.48 g, 0.032 moL) in CH_2Cl_2 (25 mL) was added dropwise to a well stirred mixture of 1-(2-ethylphenyl)hydrazono-2-oxopropionaldehyde **2**[6](6.0 g, 0.0316 moL) in CH_2Cl_2(75 mL) and 50% aqueous NaOH (32 mL) containing 0.75 g of benzyltriethylammonium chloride. The mixture was stirred for 18 h, then water (100 mL) was added, followed by extractions with CH_2Cl_2 (3x25 mL). The

combined organic phase was dried (Na_2SO_4) and evaporated to dryness, yielding 8.5 g (96%) of N-benzyl-N-arylhydrazone. The intermediate thus obtained (3.0 g, 0.011 moL) was taken up in ethanol (20 mL) and transferred to a glass pressure-reactor. 98% Hydrazine hydrate (8 mL) was added, followed by dropwise addition of conc. hydrochloric acid (4 mL) (*CAUTION!*) under stirring. The closed reactor was heated at 95-100°C for 8 h. Upon cooling, the reaction mixture was poured to water (120 mL), extracted with CH_2Cl_2 (4x40 mL) and dried (Na_2SO_4). The solution was evaporated and the residue was distilled under vacuum to yield N-benzyl-N-(2-ethylphenyl)hydrazine **3** (2.06 g, 85%), which was used in the next step. ^1H NMR ($CDCl_3$): δ 1.2 (t, 3H, J=7 Hz), 2.7 (q, 2H, J=7 Hz), 3.5 (bs, 2H), 4.0 (s, 2H), 6.7-7.2 (m, 9H).

9-Benzyl-8-ethyl-4,9-dihydro-3H-pyrano[3,4-b]indole-1-one 4

(2-Oxo-tetrahydro-3-furyl)glyoxylic acid ethyl ester[11](2.2 g, 0.011 moL), 2N H_2SO_4 (15 mL) and conc. H_2SO_4 (1.5 mL) were heated to 100°C for 6 h. The cooled reaction mixture was then neutralized by the addition of solid $NaHCO_3$. N-benzyl-N-(2-ethylphenyl)hydrazine **3** (2.06 g, 0.009 moL) in DMF (15 mL) was then added, and the reaction mixture was kept overnight under stirring at pH 7 by *dropwise* addition of conc. hydrochloric acid. The mixture was poured to water (200 mL), extracted with CH_2Cl_2 (4x50 mL), dried (Na_2SO_4) and the solvent concentrated in vacuo. A steady stream of $HCl_{(g)}$ was bubbled into a solution of the crude hydrazone in DMF (15 mL) for *ca.* 1 h. The reaction mixture was then kept closed for 24 h, poured to water (150 mL), extracted with CH_2Cl_2 (4x40 mL), dried (Na_2SO_4) and the solvent removed by rotary evaporation. Flash chromatography of the residue on silica gel with CH_2Cl_2 afforded 1.5 g (54%) of **4** as a solid; mp 135°C. ^1H NMR(200 MHz, $CDCl_3$) δ 1.25 (t,3H, J=7.5 Hz), 2.88 (q, 2H, J=7.5 Hz), 3.18 (t, 2H, J= 6.2 Hz), 4.64 (t, 2H, J=6.2 Hz), 6.09 (s, 2H), 6.81-7.52 (m, 8H). ^{13}H NMR(100 MHz, $CDCl_3$) δ 160.2, 139.6, 137.9, 129.2, 128.6, 127.8, 126.9, 125.2, 124.9, 124.4, 122.7, 121.1, 118.8, 68.6, 49.2, 25.4, 21.6, 15.9.

8-ethyl-4,9-dihydro-3H-pyrano[3,4-b]indole-1-one 5

0.5 g (1.64 mmoL) of lactone **4** was added in portions to a solution of anhydrous aluminium trichloride (0.88 g, 6.6 mmoL) in anisole (5 mL). The mixture was stirred at room temperature for 1.5 h, then poured to ice (50 g) and extracted with ether (3x25 mL). The organic phase was washed with water (20 mL), 5% aqueous $NaHCO_3$ (2x10 mL), dried ($MgSO_4$) and evaporated to give an oily residue, which was chromatographed on silica gel using hexane:CH_2Cl_2 (2:8) to give 0.35 g (90%) of **5**; mp 110°C. ^1H NMR(200 MHz, $CDCl_3$) δ 1.36 (t, 3H, J=7.5 Hz), 2.9 (q, 2H, J=7.5 Hz), 3.16 (t, 2H, J=6.2 Hz), 4.71 (t, 2H, J=6.2 Hz), 7.12-7.51 (m, 3H), 9.1 (bs, 1H). ^{13}C NMR(100 MHz, $CDCl_3$) δ 161.5, 137.4, 128.6, 124.9, 124.3, 123.5, 122.1, 121.1, 118.3, 69.4, 23.9, 21.5, 13.8. Anal. Calcd. for $C_{13}H_{13}NO_2$; C,72.54 ;H,6.09; N,6.51; Found: C,72.33; H,6.27; N,6.40.

2-ethylphenylhydrazine 3'

1-(2-Ethylphenyl)hydrazono-2-oxopropionaldehyde **2**[6] (3.2 g, 0.0168 moL), ethanol (45 mL) and 98% hydrazine hydrate (12 mL) were added to a glass pressure-reactor, followed by dropwise addition of conc. hydrochloric acid (6 mL) (*CAUTION!*) under stirring. The resultant mixture was heated at 95-100°C for 8 h. After cooling, the reaction mixture was poured to water (200 mL), extracted with CH_2Cl_2(4x50 mL) and dried (Na_2SO_4). Removal of the solvent and distillation under vacuum gave 1.83 g (80%) of 2-ethylphenylhydrazine[13] **3'** which was used in the next step. ^1H NMR ($CDCl_3$) δ 1.1 (t, 3H, J=7 Hz), 2.3 (q, 2H, J=7 Hz), 3.5 (bs, 2H), 5.0 (bs, 1H), 6.3-7.0 (m, 4H).

8-ethyl-4,9-dihydro-3H-pyrano[3,4-b]indole-1-one 5

(2-Oxo-tetrahydro-3-furyl)glyoxylic acid ethyl ester[11] (3.13 g, 0.0168 moL), 2N H_2SO_4 (20 mL) and conc. H_2SO_4 (2 mL) were heated to 100°C for 6 h. The cooled reaction mixture was then neutralized by the addition of solid $NaHCO_3$. 2-Ethylphenylhydrazine **3** (1.83 g, 0.0134 moL) in DMF (25 mL) was then added, and the reaction mixture was kept overnight at pH 7 by *dropwise* addition of conc. hydrochloric acid. The crude was poured to water (200 mL), extracted with CH_2Cl_2(4x50 mL), dried (Na_2SO_4) and the solvent concentrated in vacuo. A steady stream of $HCl_{(g)}$ was bubbled into the solution of the crude hydrazone in DMF (20 mL) for *ca.* 1 h. The reaction mixture was then kept closed for 24 h., poured to water (250 mL), extracted with CH_2Cl_2 (4x50 mL), dried (Na_2SO_4) and the solvent removed by rotary evaporation. Flash chromatography of the residue on silica gel with hexane:CH_2Cl_2 (2:8) afforded 1.7g (59%) of **5**; mp 110°C.

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