

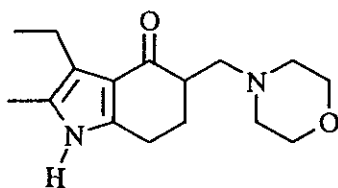
ALKYLATION OF 3-ETHYL-2-METHYL-4-OXO-4,5,6,7-TETRAHYDROINDOLE WITH BROMOESTERS: BENZENESULFONYL AS CONVENIENT NITROGEN PROTECTING GROUP

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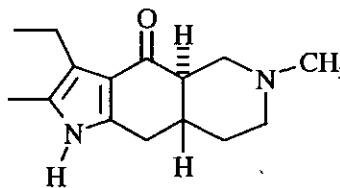
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Abstract- α -Alkylation of 3-ethyl-2-methyl-4-oxo-1*H*-4,5,6,7-tetrahydroindole (3) with bromoesters gives 3-ethyl-2-methyl-4-oxo-1*H*-4,5,6,7-tetrahydro-5-indoleacetate (5a), 3-ethyl-2-methyl-4-oxo-1*H*-4,5,6,7-tetrahydro-5-indole-2-propionate (5b), and 3-ethyl-2-methyl-4-oxo-1*H*-4,5,6,7-tetrahydro-5-indole-3-propionate (6).

As part of our research^{1,2} on the synthesis and pharmacology of analogues of the well established antipsychotics molindone (1)³ and piquindone (2),⁴ we have investigated the preparation of 2-methyl-3-ethyl-4-oxo-4,5,6,7-tetrahydroindoleacetic and propionic acids (7a, 7b and 8) by alkylation of the carbanion of the 4-oxotetrahydroindole (3) with bromoesters.



1



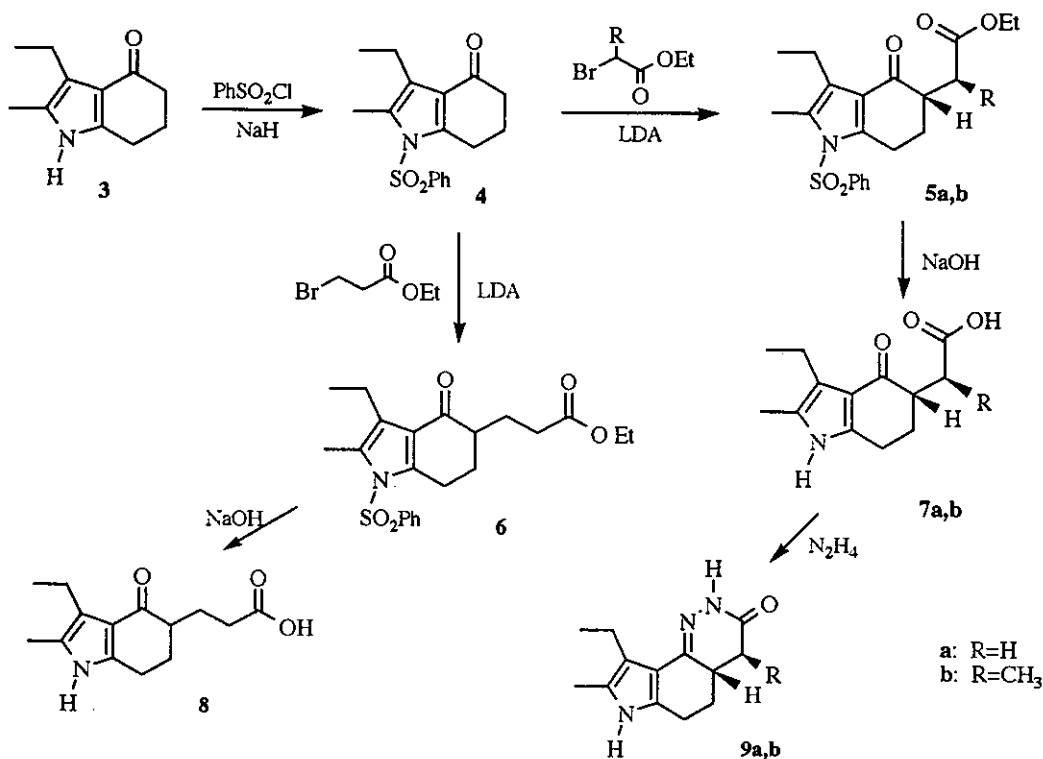
2

Protection of 2-methyl-3-ethyl-4-oxo-1*H*-4,5,6,7-tetrahydroindole (3)⁵ with benzenesulfonyl chloride in the presence of sodium hydride afforded the ketone (4) in 60% yield. Reaction of 4 with *n*-butyllithium, followed by addition of ethyl bromoacetate or ethyl 2- or ethyl 3-bromopropionate, afforded keto esters (5a), (5b) and (6) smoothly in 40-50% yields. Saponification with ethanolic sodium hydroxide and later acidification with concentrated hydrochloric acid gave the deprotected free acids (7a), (7b) and (8) as crystalline in 70-74% yields.

For identification purposes (and in connection with other research in this laboratory⁶) we also prepared 8-ethyl-9-methyl-4,4a,5,6-tetrahydroindole[4,5-c]pyridazin-3(2*H*)-ones (**9a** and **9b**) by cyclization of **7a** and **7b** with hydrazine hydrate in refluxing ethanol.

The structures of the keto acids and pyridazin-3(2*H*)-ones were supported by analytical and spectral data.

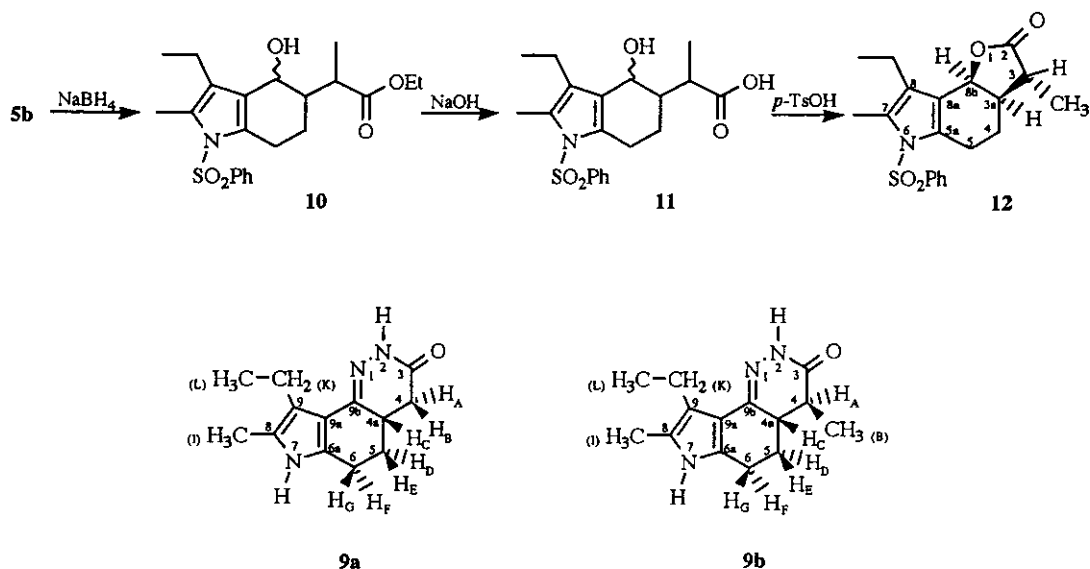
Scheme I



The stereochemistry of **5b** and **7b** was determined as follows (Scheme II). Reduction of **5b** with sodium borohydride gave the hydroxy ester (**10**), which by controlled alkaline hydrolysis and subsequent acid-catalysed lactonisation of the resulting hydroxy carboxylic acid (**11**) gave the lactone (**12**). The stereochemistry of the ring juncture and the methyl group was found to be *cis* by pmr data and analogy.⁷⁻⁹

The spatial arrangements of the protons of **9a** and of the methyl group of **9b** were determined by comparison of the ¹H-nmr data of these compounds (coupling constants in particular) with those of their benzene analogue.¹⁰ In **9a**, H_A appears in the spectrum as a triplet centred at δ 2.24 and is *trans* to H_C (J_{AC} = 15.5 Hz), while the H_B signal is part of a complex multiplet at δ 2.79-2.56. In **9b**, the signal lies slightly downfield at δ 2.39-2.21, the H_B signal is replaced by a B methyl proton doublet at δ 1.34, and the value of J_{BC} (6.4 Hz) shows that the 4-CH₃ group is *cis* to H_C.

SCHEME II



EXPERIMENTAL SECTION

Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer (KBr discs and NaCl film, \max in cm^{-1}). The ^1H -nmr spectra were obtained with a Bruker WM (250 MHz) spectrophotometer using TMS as internal standard. Microanalyses were performed with a Perkin-Elmer 240B instrument in the Microanalysis Service of the University of Santiago de Compostela; results are shown in Table 1.

1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-1*H*-4,5,6,7-tetrahydroindole (4):

To a 55% suspension of NaH in mineral oil (1.22 g, 28 mmol), stirred under nitrogen in anhydrous DMF (30 ml), was added dropwise a solution of 3-ethyl-2-methyl-4-oxo-1*H*-4,5,6,7-tetrahydroindole (3), (5 g, 28 mmol) in DMF (30 ml). After 5 h, a solution of benzenesulfonyl chloride (3.6 ml, 28 mmol) in DMF (10 ml) was added dropwise, and the resulting mixture was stirred at room temperature overnight and then for 8 h at 50°C. DMF was removed in vacuo, the residue was dissolved in ether, and the resulting solution was filtered. The filtrate was washed with water, and the organic layer was dried (Na_2SO_4) and concentrated. The residue obtained was purified by chromatography on silica gel with AcOEt/hexane (1:1) as eluant to yield 3.6 g of 4 as a white solid (60%), mp 88-90°C. Ir ν : 2933 (>N-), 1675 (>C=O), 1378-1174 (-SO₂-) cm^{-1} . ^1H -Nmr (CDCl_3): δ 7.73 (2H, dd, $J_o=6.9$ Hz, $J_m=1.5$ Hz, o-Ph), 7.65 (1H, dt, $J_o=7.3$ Hz, $J_m=1.5$ Hz, p-Ph), 7.55 (2H, dt, $J_o=7.5$ Hz, $J_m=1.6$ Hz, m-Ph), 3.13 (2H, t, $J=6.2$ Hz, pyrrole-CH₂-), 2.63 (2H, q, $J=7.4$ Hz, CH₃-CH₂-), 2.44 (2H, t, $J=6.5$ Hz, -CO-CH₂-), 2.28 (3H, s, CH₃-pyrrole), 2.09 (2H, q, $J=6.5$ Hz, -CH₂-CH₂-CH₂-), 1.03 (3H, t, $J=7.4$ Hz, CH₃-CH₂-).

Ethyl *N*-benzenesulfonyl-3-ethyl-2-methyl-4-oxo-1*H*-4,5,6,7-tetrahydro-5-indoleacetate and propionates (5a, 5b and 6). General procedure:

A solution of diisopropylamine (2.98 ml, 21 mmol) in dried THF (200 ml) was cooled to -20°C under nitrogen with stirring. A 2.5 M solution of *n*-BuLi in hexane (8.4 ml, 21 mmol) was added, and stirring is continued for 0.5 h between -20 and -10°C. The solution was cooled to -70°C and stirred for 1 h more. To this solution was added dropwise over 5-10 min 6.65 g (21 mmol) of 4 in THF (60 ml). Stirring was continued for 0.5 h at -70°C. A solution of the bromoester (21 mmol) in THF (20 ml) was then added dropwise over 5-10 min. After 15 min at -70°C the cooling bath was removed and the reaction mixture was allowed to warm to room temperature under nitrogen over 18 h. THF was evaporated and the residue was dissolved in AcOEt. The resulting solution was washed with water, 5% NaHCO₃ and 5% HCl and dried (Na₂SO₄), and the solvent was evaporated to give the crude product, which was purified by chromatography on silica gel with toluene as eluant to give the desired products (5a, 5b and 6) in 42-52% yield (Table 2).

3-Ethyl-2-methyl-4-oxo-1*H*-4,5,6,7-tetrahydro-5-indole-acetic and propionic Acids (7a, 7b and 8). General procedure:

A mixture of ester (5a, 5b or 6 (3.7 mmol)) in ethanol (15 ml) and 15% ethanolic NaOH (5 ml, 19 mmol) was stirred at reflux temperature. After 3 h the solution was concentrated, the residue was dissolved in water and washed with methylene chloride, and the aqueous layer was acidified to pH 3 with conc. HCl. The resulting precipitate was filtered off and recrystallized from methanol to give 7a, 7b or 8 in 70-74% yield (Tables 1 and 2).

3(2*H*)-Pyridazinones (9a and 9b). General procedure:

98% Hydrazine hydrate (0.4 ml, 8 mmol) was added to acid (7a or 7b) (4.2 mmol) in ethanol (25 ml), and the mixture was refluxed for 80 h. After cooling, the solid precipitated was collected and recrystallized from isopropyl alcohol to afford white crystals of 9a (56% yield; mp 220-221°C) or 9b (50% yield; mp 215-217°C).

Ir: 9a, ν = 3245 (amide NH), 2920 (>NH), 1637 (NCO), 1608 (C=C) cm⁻¹; 9b, ν = 3276 (amide NH), 2952-2925 (pyrrole NH), 1636 (NCO), 1608 (C=C) cm⁻¹.

¹H-Nmr (CDCl₃): 9a, δ 8.29 (1H, s, pyridazinone NH), 7.70 (1H, s, pyrrole NH), 2.79-2.56 (4H, m, H₆, H_{4*cis*}, H_{4*o*}), 2.65 (2H, q, J=7.4 Hz, CH₃-CH₂-), 2.24 (1H, t, J=15.5 Hz, H_{4*trans*}), 2.17 (3H, s, CH₃-pyrrole), 2.14 (1H, m, H_{5*ec*}), 1.68 (1H, m, H_{5*ax*}), 1.10 (3H, t, J=7.4 Hz, CH₃-CH₂-). 9b, δ 8.26 (1H, s, pyridazinone NH), 7.63 (1H, s, pyrrole NH), 2.74-2.56 (4H, m, CH₃-CH₂-, H₆), 2.39-2.21 (3H, m, H₄, H_{4*a*}, H_{5*ec*}), 2.17 (3H, s, CH₃-pyrrole), 1.64 (1H, m, H_{5*ax*}), 1.34 (3H, d, J=6.4 Hz, CH₃-CH), 1.10 (3H, t, J=7.4 Hz, CH₃-CH₂-).

Ethyl *N*-benzenesulfonyl-3-ethyl-4-hydroxy-2-methyl-1*H*-4,5,6,7-tetrahydro-5-indole-2'-propionate (10):

A solution of 5b (150 mg, 0.36 mmol) in ethanol (2 ml) was cooled to 25°C, sodium borohydride (0.28 mg, 0.72 mmol) was added with stirring, and after standing for 24 h at 25°C, the reaction mixture was poured into water (5 ml) and extracted with methylene chloride. The organic layer was drawn off and dried (Na₂SO₄), and the solvent was evaporated to leave an oily residue (150 mg) which was purified by chromatography on silica gel with AcOEt/hexane

(1:1) as eluant to yield 100 mg of **10** as a white solid (65%), mp 112-115°C. Ir ν : 3335 (-OH), 1734 (COOH), 1378-1174 (-SO₂-) cm⁻¹. ¹H-Nmr (CDCl₃): δ 7.58 (5H, m, Ph), 4.85 (1H, d, J=6.5 Hz, H₄), 4.15 (2H, q, J=7.1 Hz, -CH₂-O-), 3.50 (1H, m, >CH-CH₃), 2.70 (2H, m, H₇), 2.51 (2H, q, J=7.4 Hz, CH₃-CH₂-pyrrole), 2.32 (1H, m, H_{6ec}), 2.25 (3H, s, CH₃-pyrrole), 1.80 (2H, m, H₅, H_{6ax}), 1.25 (6H, m, CH₃-CH₂-O-, CH₃-CH), 0.97 (3H, t, J=7.4 Hz, CH₃-CH₂-pyrrole).

***N*-Benzenesulfonyl-3-ethyl-4-hydroxy-2-methyl-1*H*-4,5,6,7-tetrahydro-5-indole-2'-propionic acid (11):**

A mixture of hydroxy ester (**10**) (100 mg, 0.24 mmol) in ethanol (2 ml) and 5% ethanolic NaOH (0.2 ml, 2.5 mmol) was stirred at reflux temperature. After 24 h, the solution was concentrated and the residue was dissolved in water and treated with methylene chloride. The aqueous layer was acidified to pH 2 with conc. HCl and extracted with methylene chloride, and the organic extract was dried (Na₂SO₄) and the solvent was evaporated to give 60 mg of an oily residue which was used in the next step without further purification. Ir ν : 3788 (-OH), 2931 (>N-), 1708 (COOH), 1366-1180 (-SO₂-) cm⁻¹.

***N*-Benzenesulfonyl-3,7-dimethyl-8-ethyl-2-oxo-6*H*-2,3,3a,4,5,8b-hexahydrofuro[2,3-*e*]indole (12):**

A mixture of **11** (60 mg, 0.15 mmol) and benzene (10 ml) with a catalytic amount of *p*-toluenesulphonic acid was refluxed in a Dean-Stark apparatus for 1 h. After cooling, the reaction mixture was washed with 5% NaHCO₃ and water, the organic layer was dried (Na₂SO₄), and the solvent was evaporated. The oily residue was purified by chromatography on silica gel with AcOEt/hexane (1:1) to yield 40 mg of **12** (69%), mp 102-104°C. Ir ν : 2926 (>N-), 1770 (COO-), 1368-1180 (-SO₂-) cm⁻¹. ¹H-Nmr (CDCl₃): δ 7.58 (5H, m, Ph), 5.37 (1H, d, J=6.1 Hz, H₉), 2.90 (2H, m, H₅), 2.46-2.33 (4H, m, H₃, H_{3a}, CH₃-CH₂-), 2.29 (3H, s, CH₃-pyrrole), 1.87 (2H, m, H₄), 1.26 (3H, dd, J=7.0 Hz, J'=7.3 Hz, *cis* CH₃-CH), 1.06 (3H, t, J=7.4 Hz, CH₃-CH₂).

Table 1: Microanalyses

Compd	Molecular Formula	Calcd / Found		
		C	H	N
4	C ₁₇ H ₁₉ NO ₃ S	64.33 / 64.50	6.03 / 6.11	4.41 / 4.49
7a	C ₁₃ H ₁₇ NO ₃	66.36 / 66.71	7.28 / 7.12	5.95 / 5.80
7b	C ₁₄ H ₁₉ NO ₃	67.45 / 67.12	7.68 / 7.82	5.62 / 5.79
8	C ₁₄ H ₁₉ NO ₃	67.45 / 67.59	7.68 / 7.50	5.62 / 5.37
9a	C ₁₃ H ₁₇ N ₃ O	67.53 / 67.75	7.36 / 7.49	18.18 / 18.01
9b	C ₁₄ H ₁₉ N ₃ O	68.57 / 68.66	7.75 / 7.70	17.14 / 17.32
12	C ₂₀ H ₂₃ NO ₄ S	64.32 / 64.50	6.21 / 6.35	3.75 / 3.49

Table 2

3-Ethyl-2-methyl-4-oxo-1*H*-4,5,6,7-tetrahydro-5-indole acetic and propionic acids (7a, 7b and 8) and their *N*-benzenesulfonyl ethyl esters (5a, 5b and 6)

Compd	Yield (%)	mp (°C)	Molecular Formula	Ir (film or KBr) ν (cm ⁻¹)	¹ H-nmr (δ in ppm). ^a In CDCl ₃ , ^b In Pyridine- <i>d</i> ₅ .
5a	49	oil	C ₂₁ H ₂₅ NO ₅ S	1732 (COOEt), 1670 (CO), 1374-1176 (SO ₂)	7.62 (5H, m), 4.16 (2H, q, J=7.1 Hz), 3.40 (1H, ddd, J=2.8, 5.0 and 18.2 Hz), 3.00 (3H, m), 2.61 (2H, q, J=7.4 Hz), 2.20 (5H, m), 1.90 (1H, m), 1.26 (3H, t, J=7.1 Hz), 1.01 (3H, t, J=7.4 Hz) ^a
5b	42	oil	C ₂₂ H ₂₇ NO ₅ S	1733 (COOEt), 1668 (CO), 1373-1174 (SO ₂)	7.64 (5H, m), 4.17 (2H, q, J=7.1 Hz), 3.45 (1H, m), 3.13 (1H, t, J=6.1 Hz), 2.63 (2H, m), 2.43 (2H, t, J=6.5 Hz), 2.28 (3H, s), 2.11 (1H, m), 1.82 (1H, m), 1.20 (6H, m), 1.03 (3H, t, J=7.4 Hz) ^a
6	52	oil	C ₂₂ H ₂₇ NO ₅ S	1732 (COOEt), 1668 (CO), 1372-1193 (SO ₂)	7.60 (5H, m), 4.12 (2H, q, J=7.1 Hz), 3.31 (1H, dd, J=4.9 and 18.3 Hz), 3.01 (1H, ddd, J=5.1, 9.5 and 18.3 Hz), 2.60 (2H, q, J=7.4 Hz), 2.44 (2H, t, J=7.7 Hz), 2.36 (1H, m), 2.26 (3H, s), 2.17 (2H, m), 1.87 (1H, m), 1.75 (1H, dt, J=7.7 and 14.0 Hz), 1.24 (3H, t, J=7.1 Hz), 1.02 (3H, t, J=7.4 Hz) ^a
7a	74	231-232	C ₁₃ H ₁₇ NO ₃	2958 (NH), 1711 (COOH), 1618 (CO)	11.44 (1H, s), 3.32 (1H, dd, J=4.7 and 16.1 Hz), 3.05 (1H, m), 2.79 (4H, m), 2.45 (1H, dd, J=8.4 and 16.1 Hz), 2.14 (3H, s), 2.03 (1H, m), 1.95 (1H, dq, J=5.3 and 11.5 Hz), 1.24 (3H, t, J=7.4 Hz) ^b
7b	70	205-206	C ₁₄ H ₁₉ NO ₃	2963 (NH), 1718 (COOH), 1616 (CO)	10.87 (1H, s), 3.43 (1H, dq, J=3.8 and 7.1 Hz), 2.89 (1H, m), 2.57 (2H, m), 2.53 (2H, q, J=7.4 Hz), 1.96 (1H, m), 1.95 (3H, s), 1.86 (1H, m), 1.13 (3H, d, J=7.1 Hz), 0.98 (3H, t, J=7.4 Hz) ^b
8	70	235-239	C ₁₄ H ₁₉ NO ₃	2957 (NH), 1700 (COOH), 1616 (CO)	9.20 (1H, s), 3.52 (1H, m), 2.80 (5H, m), 2.43 (2H, m), 2.15 (4H, m), 1.95 (2H, m), 1.27 (3H, t, J=7.3 Hz) ^b

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