

# SYNTHESIS OF SOME NEW INDENO-INDOLES

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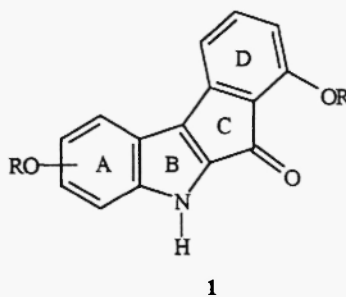
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**Abstract:** The synthesis of indeno-indoles in three steps from indanones is reported

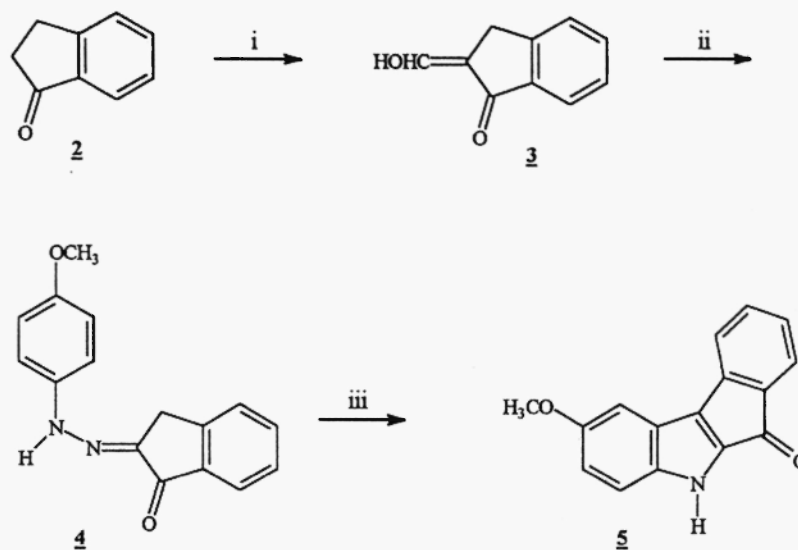
## Introduction

Condensed indolic ring systems are of interest due to their biological effects <sup>(1)</sup>. We present here the synthesis of some new indeno-indoles 1 via a Fischer indole synthesis <sup>(2)</sup>. Construction of the arylhydrazones was readily achieved by the Japp-Klingemann reaction <sup>(3)</sup> starting from  $\alpha$ -hydroxymethylidene ketones.



## Chemistry

In our efforts to develop a synthetic route to the tetracyclic compounds 1, indan-1-one 2 has been used as a readily available model compound (Scheme 1).

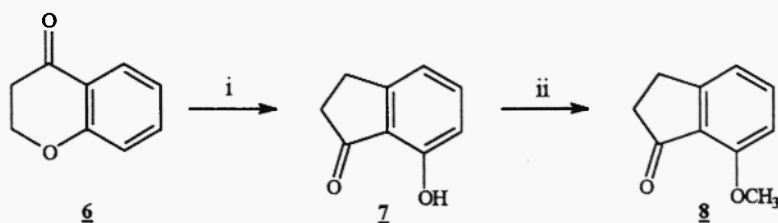


*Reagents and conditions:* i,  $\text{HCO}_2\text{Et}$ ,  $\text{MeONa}$ , toluene; ii,  $p\text{-MeO-Ph-N}_2^+$ ,  $\text{CH}_3\text{CO}_2\text{Na}$ ,  $\text{MeOH}$ ; iii,  $\text{THF/HCl}$  (10:1), reflux.

Scheme 1

The Japp-Klingemann reaction of  $\alpha$ -hydroxymethylidene derivative **3** with the diazonium salt of the para-anisidine lead to the arylhydrazone compound **4** in high yield. Initial attempts to carry out the cyclisation of **4** was problematic. Application of the standard Fischer reaction conditions to arylhydrazone **4** led mainly to resinification. Success was achieved through a protocol which involved the use of a mixture of concentrated hydrochloric acid and tetrahydrofuran in the proportion 1:10.

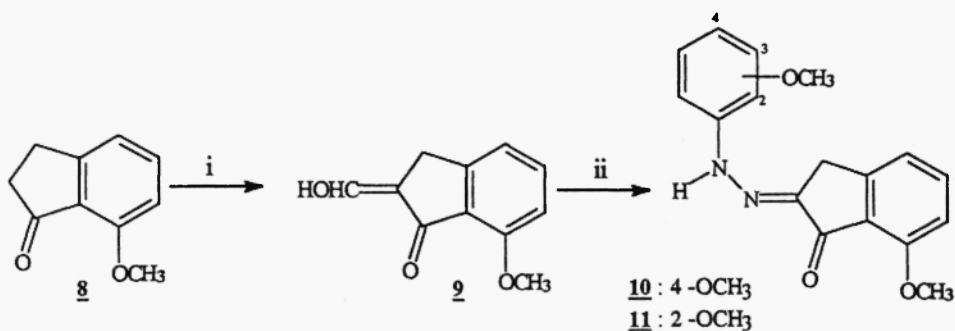
The same route was applied to 7-methoxyindan-1-one **8** which was obtained according to the method described by Loewenthal and Schatzmiller<sup>(4)</sup> (Scheme 2).



*Reagents and conditions:* i,  $\text{AlCl}_3$ ,  $\text{NaCl}$ ; ii,  $(\text{H}_3\text{C})_2\text{SO}_4$ ,  $\text{NaOH}$ .

Scheme 2

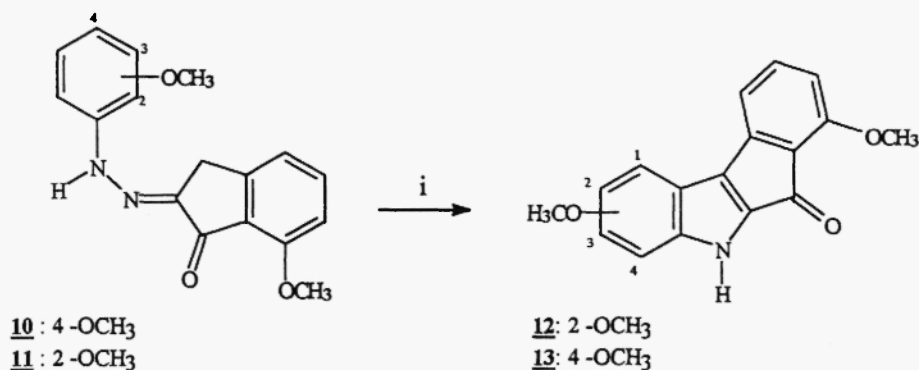
The 2-hydroxymethylidene-7-methoxyindan-1-one **9** was transformed into the hydrazones **10** and **11** in good yield via a Japp-Klingemann reaction (Scheme 3).



Reagents and conditions: i, HCO<sub>2</sub>Et, MeONa, toluene; ii, MeO-Ph-N<sub>2</sub><sup>+</sup>, CH<sub>3</sub>CO<sub>2</sub>Na, MeOH.

Scheme 3

The treatment of compounds **10** and **11** with THF/HCl 10:1 afforded respectively the desired tetracyclic structures **12** and **13** in high yield (Scheme 4).



Reagents and conditions: i: THF/HCl (10:1), reflux.

Scheme 4

## Experimental section

$^1\text{H}$  NMR Spectra were recorded using a 250 Mhz Bruker spectrometer for solutions in  $\text{CDCl}_3$  unless otherwise stated.  $\delta$  Values quoted relatives to internal  $\text{CDCl}_3$  and  $J$  values are given in Hz. Mps were determined on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were performed on a Carlo Erba elemental analyser.

### 7-Methoxyindan-1-one 8

Chroman-4-one 6 (74g, 0.05 mol), melted by warming to  $60^\circ\text{C}$ , was added dropwise in 10 min with stirring to a partial melt obtained from aluminium trichloride (410g, 3 mol) and sodium chloride (41g, 0.7 mol) at  $160^\circ\text{C}$ . After the addition, the temperature was raised to  $200^\circ\text{C}$  for 20 min. The mixture was cooled to room temperature and the resulting semisolid was added in portions with stirring to concentrated hydrochloric acid (200 ml) and ice. The solid was filtered off, suspended in concentrated sodium chloride solution (1 l) and steam distilled. The 7-hydroxyindan-1-one 7 crystallised in the receiver and was used without further purification. Ketone 7 (17g, 0.11 mol) was suspended in tetrahydrofuran (60 ml) and aqueous sodium hydroxide (10% w/v, 80 ml) and while stirring dimethyl sulfate (17 ml) was added with the temperature kept at  $50\text{--}60^\circ\text{C}$ . Two more additions of sodium hydroxyde solution (50 ml) and of dimethyl sulfate (9 ml) were made. The mixture was heated under reflux for 15 min. After cooling, extraction with dichloromethane gave a residue which was recrystallised from cyclohexane to give the desired ketone 8.

(65%), mp  $108^\circ\text{C}$  (cyclohexane) (Found: C, 72.83; H, 5.96.  $\text{C}_9\text{H}_8\text{O}_2$  requires C, 72.96; H, 5.89%);  $\delta_{\text{H}}$  2.72 (2H, m), 3.16 (2H, m), 3.94 (3H, s), 6.76 (1H, d,  $J$  6.2), 6.95 (1H, d,  $J$  6.2) and 7.42 (1H, m).

### General procedure for preparation of the hydroxymethylidene derivatives 3 and 9.

A mixture of indanone (0.15 mol) and methyl formate (18.2 g, 0.30 mol) was slowly added to a suspension of sodium methoxide (16.3 g, 0.30 mol) in toluene (300 ml). After 24 hours stirring, water (300 ml) was added. The organic layer was washed 3 times with aqueous sodium hydroxide (10% w/v, 150 ml). The combined aqueous layers were brought to pH 6 with concentrated hydrochloric acid and extrated with 3 times with ether (150 ml). The combined organic layers were washed with brine (200 ml), dried and concentrated under reduced pressure.

### 2-Hydroxymethylidenindan-1-one 3

(58%), mp  $112^\circ\text{C}$  (cyclohexane) (Found: C, 74.83; H, 5.16.  $\text{C}_{10}\text{H}_8\text{O}_2$  requires C, 75.00; H, 5.00 %);  $\delta_{\text{H}}$  3.58 (2H, s), 7.52 (4H, m) and 10.82 (1H, s).

**2-Hydroxymethylidene-7-methoxyindan-1-one 9**

(58%), mp 158°C (methanol) (Found: C, 69.23; H, 5.42.  $C_{11}H_{10}O_3$  requires C, 69.45; H, 5.30 %);  $\delta_H$  3.52 (2H, s), 3.95 (3H, s), 7.46 (3H, m) and 10.08 (1H, s).

**General procedure for preparation of the arylhydrazones 4, 10 and 11 (Japp-Klingemann condensation).**

To a well-stirred solution of sodium acetate (8.2 g, 0.1 mol) in water (60 ml) was added the hydroxymethylidene derivative (0.04 mol) in methanol (100 ml) and, after 10 min., a solution of the arenediazonium chloride (0.05 mol) from diazotization of the corresponding aniline. The phenylhydrazone precipitated as a orange solid, and was collected by filtration and washed with water.

**2-(4'-Methoxyphenylhydrazono)-indan-1-one 4**

(95%), mp 220°C (methanol) (Found: C, 72.33; H, 5.22; N, 10.58.  $C_{16}H_{14}N_2O_2$  requires C, 72.17; H, 5.25; N, 10.53%);  $\delta_H$  (DMSO  $d_6$ ) 3.77 (2H, s), 3.81 (3H, s), 6.90 (2H, d,  $J$  8.9), 7.25 (2H, d,  $J$  8.9), 7.43 (1H, t,  $J$  7.1), 7.55 (2H, m), 7.85 (1H, d,  $J$  7.7) and 13.54 (1H, s).

**7-Methoxy-2-(4'-methoxyphenylhydrazono)-indan-1-one 10**

(93%), mp 170°C (methanol) (Found: C, 68.87; H, 5.51; N, 9.36.  $C_{17}H_{16}N_2O_3$  requires C, 68.92; H, 5.40; N, 9.46%);  $\delta_H$  (DMSO  $d_6$ ) 3.72 (2H, s), 3.81 (3H, s), 4.00 (3H, s), 6.87 (3H, m), 7.08 (1H, d,  $J$  7.5), 7.21 (2H, d,  $J$  8.9), 7.51 (1H, t,  $J$  7.5) and 13.70 (1H, s).

**7-Methoxy-2-(1'-methoxyphenylhydrazono)-indan-1-one 11**

(91%), mp 161-162°C (methanol) (Found: C, 69.07; H, 5.53; N, 9.35.  $C_{17}H_{16}N_2O_3$  requires C, 68.92; H, 5.40; N, 9.46%);  $\delta_H$  (DMSO  $d_6$ ) 3.68 (2H, s), 3.92 (3H, s), 3.99 (3H, s), 6.90 (4H, m), 7.06 (1H, d,  $J$  7.4), 7.55 (1H, t,  $J$  7.8), 7.76 (1H, d,  $J$  7.2) and 8.29 (1H, s).

**General procedure for preparation of the indeno-indoles 5, 12 and 13.**

The phenylhydrazone (0.01 mol) was refluxed in 30 ml of a solution of THF-HCl conc. (v/v, 10-1) for 2h. The mixture was allowed to cool temperature. The solid was collected by filtration and washed with water.

**9-Methoxy-5-oxo-6H-indeno[2,3-*b*]indole 5**

(86%), mp 234°C (methanol) (Found: C, 77.21; H, 4.37; N, 5.69.  $C_{16}H_{11}NO_2$  requires C, 77.11; H, 4.42; N, 5.61%);  $\delta_H$  (DMSO  $d_6$ ) 3.72 (3H, s), 6.93 (1H, dd,  $J$  9.1 and 3.0), 7.00 (1H, t,  $J$  7.4), 7.22 (1H, d,  $J$  9.1), 7.30 (3H, m), 7.41 (1H, d,  $J$  6.1), and 11.94 (1H, s).

**4,9-Dimethoxy-5-oxo-6*H*-indeno[2,3-*b*]indole 12**

(88%), mp 261°C (methanol) (Found: C, 72.24; H, 4.71; N, 4.93. C<sub>17</sub>H<sub>14</sub>NO<sub>3</sub> requires C, 72.86; H, 5.03; N, 5.00%);  $\delta_H$  (DMSO *d*<sub>6</sub>) 3.81 (6H, s), 6.76 (1H, d, *J* 9.0), 6.87 (1H, dd, *J* 9.2 and 2.5), 7.02 (1H, d, *J* 7.5), 7.25 (3H, m) and 11.81 (1H, s).

**4,7-Dimethoxy-5-oxo-6*H*-indeno[2,3-*b*]indole 13**

(82%), mp 252°C (methanol) (Found: C, 72.54; H, 4.93; N, 5.08. C<sub>17</sub>H<sub>14</sub>NO<sub>3</sub> requires C, 72.86; H, 5.03; N, 5.00%);  $\delta_H$  (DMSO *d*<sub>6</sub>) 3.82 (3H, s), 3.91 (3H, s), 6.78 (2H, m), 6.93 (1H, d, *J* 7.5), 7.06 (1H, t, *J* 7.5), 7.30 (3H, m) and 12.02 (1H, s).

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