# Synthesis of 2-Acetoacetyl- and 2-Oxaloacetyl-1,3-indandiones and Related Compounds

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2-Acetoacetyl- and 2-Oxaloacetyl-1,3-indandiones,
1,6-Bis(1,3-dioxo-2-indanyl)hexane-1,2,3,4,5,6-hexone, Synthesis

Claisen condensation of 2-acetyl-1,3-indandione (**1**) with ethyl acetate afforded the 2-acetoacetyl-1,3-indandione (**2**) which upon treatment with benzylamine and paraformaldehyde in a molar ratio of (1:1:2) and (1:2:4) afforded the piperidinone and the diazabicyclic derivative (**4**) and (**5**) respectively. On the other hand, Claisen condensation of **1** with diethyl oxalate yielded two products (**6**) and (**9**). The behaviour of **6** towards phenyl hydrazine, and of **9** towards selenium dioxide and double Mannich reaction were also investigated.

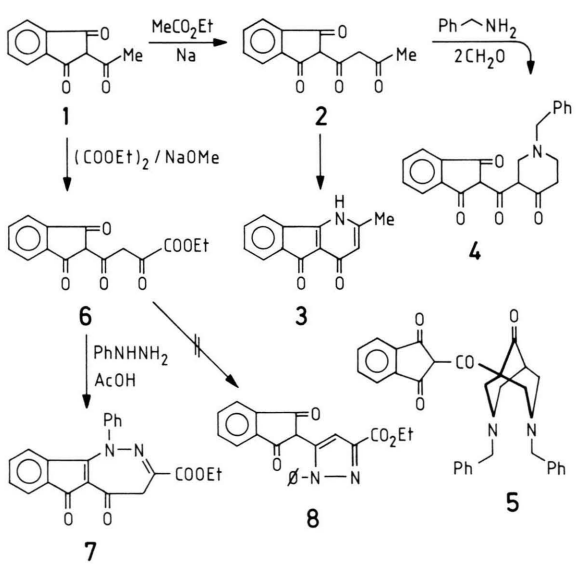
## Introduction

The interesting biological activity of 1,3-indandiones having a ketonic side chain in position 2 as blood anticoagulants and effective rodenticides [1, 2], has led to intense interest in the synthesis of 2-acyl-1,3-indandiones. In particular, much interest has centered around 2-acetyl- and 2-diarylacetyl-1,3-indandiones [2]. However, there appears to be no record of any 1,3-indandiones having a side chain at the 2-position related to $\beta$-diketones.

One of the specific objectives of this study was to synthesize 2-acetoacetyl-1,3-indandione (**2**), which, pharmacologically, is interesting in its own right. Therefore, 2-acetyl-1,3-indandione (**1**) was subjected to Claisen condensation with ethyl acetate to afford **2** in good yield. The reaction of **2** with ammonium acetate led to the formation of 2-methyl-1H-indeno-[1,2-b]pyridine-4,5-dione (**3**). The IR spectrum of **2** showed bands at 3500 (OH, enolic) and 1690 $cm^{-1}$ (CO, $\beta$-diketone). Its NMR spectrum indicated the presence of singlet absorption at $\delta$ 3.4 corresponding to ($CH_2$) of $CO \cdot C\underline{H}_2 \cdot CO$.

In connection with our studies on ketonic Mannich bases related to 1,3-indandione [3, 4], and related compounds [5, 6] it appeared to us, that compound **2** may function as an intermediate in synthetic routes based on the Mannich reaction, and directed towards 1,3-indandiones incorporated with other ring systems. Therefore, compound **2** was treated with benzylamine and paraformaldehyde in a molar ratio of (1:1:2) in acetic acid to give 1-benzyl-3-[(1,3-dioxo-2-indanyl)carbonyl]piperidin-4-one (**4**). On the other hand, the same reactants in a molar ratio of (1:2:4) afforded 3,7-dibenzyl-1-[(1,3-dioxo-2-indanyl)carbonyl]-9-oxo-3,7-diazabicyclo[3.3.1]nonane (**5**). The IR spectrum of **4** and **5** showed bands at 1725 $cm^{-1}$ characteristic of $\nu_{CO}$ piperidone and $\nu_{CO}$ bispidinone, respectively. The NMR spectrum of **4** showed a multiplet at $\delta$ 3.5 corresponding to three methylene protons of the piperidone ring. On the other hand, the NMR spectrum of **5** showed a singlet at $\delta$ 1.8 corresponding to 1-H of the diazabicyclic ring.

That the acetonyl fragment of the acetoacetyl group is involved in the formation of




Scheme 1.

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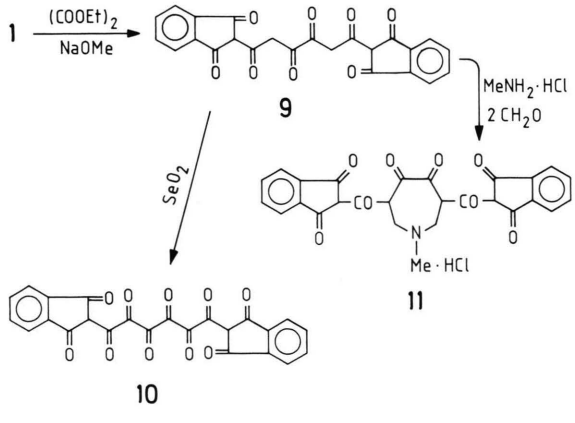
the $\gamma$-piperidone or bispidinone ring systems in the course of a double Mannich reaction, is in line with many reported cases which have been reviewed by Blicke [7] and Tramontini [8], and with our recent studies on double Mannich reaction [9, 10].

Claisen condensation of **1** with diethyl oxalate in presence of sodium methoxide led to the formation of ethyl(2-oxaloacetyl)-1,3-indandione (**6**), the structure of which was supported by the IR spectrum which showed a band at 1755 $cm^{-1}$ assigned to $\nu_{CO}$ ($\alpha$-keto ester). Reaction of **6** with phenylhydrazine gave 3-ethoxycarbonyl-1-phenyl-4,5-dihydroindeno-[1,2-c]pyrazolo[1,2]diazepin-5,6-dione (**7**), instead of the pyrazole **8**. The formation of **7** is in analogy with the reported formation of indeno[1,2-c][1,2]-diazepinones from hydrazines and 2-($\alpha$-phenacyl)-1,3-indandione [11] and related compounds [3]. The IR spectrum of **7** showed a band at 1690 $cm^{-1}$ ($\nu_{CO}$, indenone) and lacked absorption bands typical for indandione; its NMR spectrum showed a singlet corresponding to two protons (4-H).

Condensation of **1** with diethyl oxalate in a molar ratio of 2:1 in presence of sodium methoxide afforded 1,6-bis(1,3-dioxo-2-indanyl)-1,3,4,6-hexanetetrone (**9**). The formation of **9** is in line with the work of Finar [12] on the condensation of diethyl oxalate with acetophenone. Oxidation of compound **9** with selenium dioxide took place smoothly and afforded 1,6-bis(1,3-dioxo-2-indanyl)hexane-1,2,3,4,5,6-hexone (**10**). A double Mannich reaction on **9** with methylamine hydrochloride and formalin in a molar ratio of 1:1:2 led to the formation of hexahydro-1-methyl-3,6-bis[(1,3-dioxo-2-indanyl)carbonyl]-2H-azepin-4,5-dione (**11**). Its IR spectrum showed absorptions at 2915 $cm^{-1}$, characteristics of ($CH_3$–N), and 1415 $cm^{-1}$ (C–N, stretch).




Scheme 2.

## Experimental

All melting points (°C) are uncorrected and were taken in a Gallenkamp electric melting point apparatus. IR spectra were performed on a Unicam SP 2000 Infrared Spectrophotometer using KBr. $^1H$ NMR spectra were obtained in $CDCl_3$ solutions with a Varian model "A-60".

*2-Acetoacetyl-1,3-indandione* (**2**)

A suspension of **1** (1.9 g, 0.01 mole) in ethylacetate (50 ml, 0.57 mole) was slowly added to sodium sand (4 g, 0.17 g atom). The reaction mixture was refluxed for 5 h, the excess ethylacetate was distilled. The reaction mixture was poured onto ice-cold water, acidified with diluted hydrochloric acid and the resulting solid product was recrystallized from ethanol to give 1.27 g (55%), m.p. 125 °C. IR: 3550–3300 (OH, enolic), 1720 ($\nu_{CO}$, indandione), 1690 $cm^{-1}$ (CO, $\beta$-diketone); $^1H$ NMR ($CDCl_3$): $\delta$ = 2.2 (s, 3H, CO·C<u>H</u>$_3$), 2.5 (s, 1H, H-2 of indandione), 3.4 (s, 2H, CO–C<u>H</u>$_2$–CO), 7.3 (m, 4H, aromatic protons).

$C_{13}H_{10}O_4$ (230.2)
Calcd C 67.82 H 4.38,
Found C 67.64 H 4.35.

*2-Methyl-1H-indenol[1,2-b]pyridine-4,5-dione* (**3**)

A mixture of **2** (0.5 g, 0.0022 mole) and ammonium acetate (1 g, 0.012 mole) in glacial acetic acid (15 ml) was refluxed for 4 h. After cooling the reaction mixture was poured onto water (30 ml). The solid which separated was recrystallized from benzene to give 0.37 g of a brown powder (80%), m.p. 260 °C (decomp). IR: A very weak broad band at 3350–3120 (N–H, stretch), 1690 ($\nu_{CO}$ of $\alpha,\beta$-unsaturated ketone) and 1320 $cm^{-1}$ ($\nu_{C-N}$).

$C_{13}H_9NO_2$ (211.2)
Calcd C 73.92 H 4.30 N 6.63,
Found C 73.79 H 4.23 N 6.57.

*1-Benzyl-3-[(1,3-dioxo-2-indanyl)-carbonyl]piperidine-4-one* (**4**)

A mixture of **2** (2.3 g, 0.01 mole), benzylamine (1.1 g, 0.01 mole) and paraformaldehyde (0.6 g, 0.02 mole) in acetic acid (80 ml) was heated to boiling, then left overnight at room temperature. The reaction mixture was basified (pH 7.5) using sodium hydroxide solution (20%) and the solid that obtained

was recrystallized from ethanol to give 1.19 g (33%), m.p. 170 °C. IR: 3550–3300 (OH, enolic), 1725 ($\nu_{CO}$, piperidone), 1720 (CO, indandione), 1690 $cm^{-1}$ (CO, $\beta$-diketone); $^1H$ NMR ($CDCl_3$): $\delta$ = 1.35 (s, 2H, $C\underline{H}_2-C_6H_5$), 1.90 (s, 1H, methine of piperidone), 2.5 (s, 1H, 2-H of indandione), 3.5 (m, 6H, $C\underline{H}_2$-3 of piperidone), 7.3 (m, 9H, aromatic protons).

$C_{22}H_{19}NO_4$ (361.4)
Calcd C 73.11 H 5.30 N 3.88,
Found C 73.02 H 5.19 N 3.77.

*3,7-Dibenzyl-1-[(1,3-dioxo-2-indanyl)carbonyl]-9-oxo-3,7-diazabicyclo[3.3.1]nonane* (**5**)

A mixture of **2** (2.3 g, 0.01 mole), benzylamine (2.2 g, 0.02 mole) and paraformaldehyde (1.2 g, 0.04 mole) in acetic acid (80 ml) was heated to boiling, then left overnight at room temperature. The reaction mixture was worked up as above. The precipitated product was filtered off and recrystallized from ethanol to give 1.48 g (30%), m.p. 142 °C. IR: 3550–3300 (OH, enolic), 1725 ($\nu_{CO}$, bispidinone), 1720 ($\nu_{CO}$, indandione) and 1650–1540 $cm^{-1}$ ($\nu_{CO}$, $\beta$-diketone); $^1H$ NMR ($CDCl_3$): $\delta$ = 1.35 (s, 4H, $2C\underline{H}_2-C_6H_5$), 1.8 (s, 1H, 1-H, methine of diazabicyclic ring), 2.5 (s, 1H, 2-H of indandione), 3.5 (m, 8H, $C\underline{H}_2$-4 of diazabicyclic ring system) and 7.3 (m, 14H, aromatic protons).

$C_{31}H_{28}N_2O_4$ (492.6)
Calcd C 75.58 H 5.73 N 5.69,
Found C 75.46 H 5.66 N 5.58.

*Ethyl(2-oxaloacetyl)-1,3-indandione* (**6**)

To a stirred solution of **1** (7.5 g, 0.04 mole) and diethyl oxalate (excess; 0.1 mole) there was added dropwise a solution of sodium methoxide (4 g, 0.074 mole). The mixture was refluxed for4 h, cooled and then acidified with acetic acid (3%) to give a yellow solid which was recrystallized from benzene to give 9.92 g (86%), m.p. 153 °C (decomp.). IR: 3550–3300 (OH, enolic), 1755–1740 ($\nu_{CO}$, $\alpha$-keto ester), 1720 ($\nu_{CO}$, indandione) and 1650–1540 $cm^{-1}$ ($\nu_{CO}$, $\beta$-diketone).

$C_{15}H_{12}O_6$ (288.3)
Calcd C 62.50 H 4.20,
Found C 62.38 H 4.14.

*3-Ethoxycarbonyl-1-phenyl-4,5-dihydroindeno[1,2-c][1,2]-diazepin-5,6-dione* (**7**)

A mixture of **6** (2.9 g, 0.01 mole) and phenylhydrazine (1.08 g, 0.01 mole) in glacial acetic acid (40 ml) was refluxed for 5 h. After cooling, the reaction mixture was poured onto water (80 ml). The solid which separated was recrystallized from ethanol to give 3.10 g orange crystals (86%), m.p. 131 °C. IR: 1740 ($\nu_{CO}$, $\alpha,\beta$-unsaturated ester), 1690 (CO, indenone), 1620 ($\nu_{CO}$, $\alpha,\beta$-unsaturated ketone), 1260 $cm^{-1}$ ($\nu_{CN}$); $^1H$ NMR ($CDCl_3$): $\delta$ = 2.45 (s, 2H, 4-H), 3.9 (q, 4H, $C\underline{H}_2-CH_3$), 7.3 (m, 9H, aromatic protons).

$C_{21}H_{16}N_2O_4$ (360.4)
Calcd C 69.98 H 4.48 N 7.78,
Found C 69.77 H 4.36 N 7.69.

*1,6-Bis(1,3-dioxo-2-indanyl)-1,3,4,6-hexantetrone* (**9**)

To a stirred solution of **1** (7.5 g, 0.04 mole) and diethyl oxalate (2.9 g, 0.02 mole) there was added dropwise a solution of sodium methoxide (4 g, 0.074 mole). The reaction mixture was refluxed for 4 h, then worked up as described for compound **6** to give a yellow solid which was recrystallized from benzene to give 14.46 g (84%), m.p. 175 °C. IR: 3550–3300 (OH, enolic), 1730 ($\nu_{CO}$, $\alpha$-diketone), 1710 (CO, indandione), 1690–1590 $cm^{-1}$ ($\nu_{CO}$, $\beta$-diketone).

$C_{24}H_{14}O_8$ (430.4)
Calcd C 66.48 H 3.28,
Found C 66.77 H 3.19.

*1,6-Bis(1,3-dioxo-2-indanyl)hexane-1,2,3,4,5,6-hexone* (**10**)

A mixture of dioxane (3.2 ml) water (0.1 ml) and powdered selenium dioxide (1.1 g, 0.01 mole) was heated with stirring at 55 °C untill solution was complete. Compound **9** (1.7 g, 0.005 mole) was added, the mixture maintained at reflux with stirring for 4 h. It was filtered hot, the solvent removed under vacuo, and the residue recrystallized from diluted ethanol (1:1) to give 1.31 g (57%), m.p. 117 °C. IR: 3550–3300 (OH, enolic), 1800 ($\nu_{CO}$, $\alpha$-diketone), 1720 ($\nu_{CO}$, indandione), 1620–1580 $cm^{-1}$ ($\nu_{CO}$, $\beta$-diketone).

$C_{24}H_{10}O_{10}$ (458.3)
Calcd C 62.89 H 2.10,
Found C 62.72 H 2.08.

*Hexahydro-1-methyl-3,6-bis[(1,3-dioxo-2-indanyl)-carbonyl]-2H-azepin-4,5-dione* (**11**)

A mixture of **7** (1.7 g, 0.005 mole) and methylamine hydrochloride (0.3 g, 0.005 mole) and paraformaldehyde (0.3 g, 0.01 mole) in ethanol (40 ml)

was refluxed for 4 h, left overnight at room temperature. The precipitated product was filtered off, purified through boiling several times with ethanol followed by filtration to give a pure analytical sample; 1.57 g (60%), m.p. >300 °C. IR: 2915 ($CH_3$–N), a broad band 1730–1650 $cm^{-1}$ characteristic of ($\nu_{CO}$, $\alpha$-diketone, indandione and $\beta$-diketone) and 1415 $cm^{-1}$ ($\nu_{C-N}$).

$C_{27}H_{20}NO_8Cl$ (521.9)

| | | | |
|---|---|---|---|
| Calcd | C 62.13 | H 3.86 | N 2.68, |
| Found | C 62.04 | H 3.78 | N 2.59. |

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