A Study on the Mannich Reaction with 1,3-Indandione

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Mannich Reaction, 1,3-Indandione

Attempted Mannich reaction with the title compound **1** using morpholine and formalin led to **2** or **4** according to the reaction conditions. Whereas, on using primary amines the diindeno [1,2-b:2',1'-e]pyridine (**9–11**) were obtained, in addition to 2-methylene-1,3-indandione (**6**), in case of **10** and **11**.

However, the Mannich bases **13–15** were formed on treating 2-benzylidene-1,3-indandione with the appropriate secondary amine. The structures **2**, **9–11** were confirmed *via* unambiguous syntheses.

A search of the literature showed that the only reported case of Mannich reaction with 1,3-indandione (**1**) failed [1]. However, a number of 2-aryl- and aralkyl-2-aminomethyl-1,3-indandiones with psychopharmacological and anticoagulant activity [2], and also the pharmaceutically acceptable oxazidione [3] “2-(morpholinomethyl)-2-phenyl-1,3-indandione” were reported in the patent literature. Prompted by these reports and in continuation of our work in this area [4–8], we investigated the Mannich reaction of **1** under different conditions.

Treatment of **1** with morpholine and formalin in ethanol–acetic acid, gave a sole product which was identified as 2,2'-methylene-bis[1-(N-morpholino)-3-indenone] (**2**), and non of the expected Mannich base **3** was obtained. On the other hand, the same reaction in acetic acid medium afforded a single product which was free from nitrogen, and insoluble in most organic solvents. The structure **4** assigned to this product is based on its analytical and IR spectral data.

Formation of compound **2** instead of **3** may be rationalized on the basis of a mechanism which involves the formation of 2-methylene-1,3-indandione (**6**) and this will further react with carbanion **5** to give 2,2'-methylene-bis-1,3-indandione (**7**) (Scheme 2). Therefore, compound **2** is formed, rather than **3**, which would be obtained if **6** is attacked by morpholine instead of **5**. This is because morpholine is less nucleophilic than the carbanion **5**, and will not attack **6** as fast as the carbanion

will. In order to confirm this mechanism and structure of **2**, we prepared **7** [9] which was treated with morpholine to give **2** (Scheme 1).

The spiro compound **4** is presumably formed by a mechanism which involves the intramolecular cyclization of the prefounded species (Scheme 3).

Obviously, anion **7** is the main intermediate in the reaction sequence, and its formation is expected in line of the behaviour of dimedone [10], and our report on Mannich reaction with 5-phenylcyclohexan-1,3-dione [11].

On the other hand, when **1** was treated with methylamine and formalin, it gave 5-methyl-5H-diindeno[1,2-b:2',1'-e]pyridine-10,12(11H)-dione (**9**), the NMR spectrum of which showed signals at δ 2.50 (N–CH₃) and 3.65 cyclic (–CH₂–).

Similarly, compounds **10** and **11** were obtained on using benzylamine or ammonium acetate respectively. In its NMR spectrum compound **10** showed signals at δ 2.75 (Ph–CH₂–N) and 3.60 cyclic (–CH₂–), in addition, a singlet was observed at δ 4.90 (2H) attributable to a vinylic (=CH₂) protons, indicating the presence of 2-methylene-1,3-indandione (**6**) as a fleeting intermediate. This was also observed in case of **11**. It is therefore reasonable to assume that **6** is one of the intermediates in the reaction sequence, and that compounds **9–11** were formed *via* a mechanism which is identical to that of Scheme 2. The final step in such mechanism is the amination of **7** with primary amines to give **9–11**.

The unambiguous synthesis of compounds **9–11** by treating **7** [9] with the appropriate amine confirmed their structures. This method afforded a pure samples of **10** and **11**, whereas, **9** was identical to that obtained from **1**.

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Scheme 1

Scheme 2

In an alternative route to the diindeno-[1,2-b:2',1'-e]pyridine ring system, we prepared *N,N*-di(3-indenon-1-yl)-benzylamine (**12**), which is a possible precursor to compound **10**. Treatment of **12** with formalin afforded **10**, such reaction is in line with the work of Greenhil [12] on the reactions of enaminones with aldehydes.

It appeared therefore, that formation of Mannich bases related to **1** can be achieved by treating a preformed 2-methylene-1,3-indandione (**6**) with amines. However, our attempts to prepare such

Scheme 3

compound failed. Therefore, we prepared Mannich bases **13–15** by treatment of 2-benzylidene-1,3-indandione [13] with morpholine, piperidine or piperazine, respectively. In this type of synthesis, the aminomethyl side chain must have an aryl fragment.

Experimental

Analytical data were determined by the Micro-analytical Unit, Faculty of Science, Mansoura University. Infra-red spectra were recorded on KBr discs using a Unicam SP 2000 spectrophotometer. NMR spectra in CDCl_3 solution were obtained on a Varian EM-360 60 MHz spectrometer with TMS as an internal standard. Melting points were uncorrected.

2,2'-Methylene-bis[1-(*N*-morpholino)-3-indenone] (**2**)

(A) A solution of 1,3-indandione (**1**) (0.01 mol, 1.46 g), formalin (37%) (0.01 mol, 0.81 ml) and morpholine (0.01 mol, 0.87 ml) in ethanol (40 ml) and few drops of acetic acid, was kept at room temperature for 24 h. The solid which separated was recrystallized from ethanol to give pink crystals, m.p. 175 °C in (1.7 g) 75% yield. IR 1720 (CO of indenone) and 1370 cm^{-1} (C–N stretch.).

$\text{C}_{27}\text{H}_{26}\text{N}_2\text{O}_4$ (442.05)

Calcd C 73.28 H 5.92 N 6.33,
Found C 73.04 H 5.66 N 6.37.

(B) A solution of 2,2'-methylene-bis-1,3-indandione (**7**) (0.01 mol, 3.04 g) and morpholine (0.02 mol, 1.75 ml) in ethanol (50 ml) and few drops of acetic acid, was kept at room temperature for 24 h, then worked up as described above, m.p. 175 °C in (3.7 g) 84% yield (mixed m.p.).

3,4-Dihydro-2*H*-indeno[1,2-*b*]pyrano[3-*spiro*-2']-indan-1',3',5-trione (**4**)

A solution of **1** (0.01 mol, 1.46 g), formalin (37%) (0.01 mol, 0.81 ml) and morpholine

(0.01 mol, 0.87 ml) or piperidine (0.01 mol, 1 ml) in acetic acid (30 ml) was heated on a steam bath for 2 h. The solid product that obtained on cooling was collected, washed several times with hot alcohol to give **4** as white powder, m.p. 280 °C in (1 g) 62% yield.

$\text{C}_{20}\text{H}_{12}\text{O}_4$ (316.3)

Calcd C 75.94 H 3.83,
Found C 76.02 H 3.54.

IR 1730 (CO, indandione) and 1695 cm^{-1} (CO, indenone).

5-Methyl-5*H*-diindeno[1,2-*b*:2',1'-*e*]pyridine-10,12(11*H*)-dione (**9**), 5-benzyl-5*H*-diindeno[1,2-*b*:2',1'-*e*]pyridine-10,12(11*H*)-dione (**10**) and 5*H*-diindeno[1,2-*b*:2',1'-*e*]pyridine-10,12(11*H*)-dione (**11**)

Procedure A: From 1,3-indandione: A solution of **1** (0.01 mol, 1.46 g); formalin (37%) (0.01 mol, 0.81 ml) and (40%) methylamine (0.01 mol, 0.86 ml) or benzylamine (0.01 mol, 1.1 ml) or ammonium acetate (0.01 mol, 0.77 g) in ethanol (40 ml) and few drops of acetic acid, was kept overnight at room temperature. The reaction mixture was diluted with water (50 ml), basified to pH 8 by ammonia. The precipitated products were recrystallized from ethanol (*cf.* Table I).

Procedure B: From 2,2'-methylene-bis-1,3-indandione: A solution of **7** (10 mmol, 3.04 g) in glacial acetic acid (10 ml), (98%) methylamine (12 mmol, 0.38 g) or benzylamine (12 mmol, 1.31 g) or ammonium acetate (12 mmol, 0.93 g) in acetic acid (10 ml), was heated on a steam bath for 3 h, left to cool, diluted with water. The solid obtained was recrystallized from ethanol to give **9**, **10** and **11** in (1.95 g) 65%, (2.9 g) 77% and (2.3 g) 80% yield respectively.

Procedure C: From *N,N*-di(3-indenon-1-yl)-benzylamine (**12**): A solution of **12** (0.01 mol, 3.63 g), formalin (37%) (0.01 mol, 0.81 ml) in ethanol (40 ml), was kept overnight at room temperature. The separated product was recrystallized from ethanol to give **10** in (1.9 g) 50% yield.

Compound	Colour	M.p. [°C]	Yield [%]	Formula (mol. wt.)	Analyses (%) C	Found (calcd) H
9	brown	185	70	$\text{C}_{20}\text{H}_{13}\text{NO}_2$ (299.3)	79.98 (80.25)	4.02 (4.37)
10	greenish	238	82	$\text{C}_{26}\text{H}_{17}\text{NO}_2$ (375.4)	83.00 (83.18)	4.35 (4.56)
11	brown	278	79	$\text{C}_{19}\text{H}_{11}\text{NO}_2$ (285.3)	80.02 (79.98)	3.63 (3.89)

Table I. Diindeno[1,2-*b*:2',1'-*e*]pyridines (**9–11**).

Compound **9**: Its IR 1710 (CO of indenone), 1420 (N-CH₃) and 1375 cm⁻¹ (C-N stretch.); NMR δ 2.50 (s, 3H, N-CH₃), 3.65 (s, 2H, cyclic-CH₂) and 7.3–7.6 (m, 8H, aromatic protons).

Compound **10**: IR 1705 (CO of indenone) and 1360 cm⁻¹ (C-N stretch.); NMR δ 2.75 (s, 2H, benzylic-CH₂), 3.6 (s, 2H, cyclic-CH₂) and 7.1–7.9 (complex pattern, 13H, aromatic protons).

Compound **11**: IR broad band at 3490–3420 (NH), 1720 (CO of indenone) and 1270 cm⁻¹ (C-N stretch.); NMR δ 2.6 (s, 1H, NH), 3.55 (s, 2H, cyclic-CH₂) and 7.2–7.8 (m, 8H, aromatic protons).

Synthesis of N,N-di(3-indenon-1-yl)benzylamine (12)

A solution of **1** (0.04 mol, 5.85 g), benzylamine (0.02 mol, 2.19 ml) in ethanol (80 ml) and few drops of acetic acid, was kept overnight at room temperature. The separated solid was recrystal-

lized from ethanol to give **12** as greenish crystals, m.p. 87 °C (decomp.) in (4 g) 55% yield.

$C_{25}H_{17}NO_2$ (363.4)

Calcd C 82.62 H 4.70,

Found C 82.38 H 4.80.

IR 1710 (CO, indenone) and 1360 cm⁻¹ (C-N stretch.).

2-(N-Morpholinobenzyl)-1,3-indandione (13),
2-(N-piperidinobenzyl)-1,3-indandione (14) and
N,N'-bis(1,3-indandione-2-yl-benzyl)piperazine (15)

General procedure: A solution of 2-benzylidene-1,3-indandione (5 mmol, 1.17 g) and morpholine (5 mmol, 0.44 ml) or piperidine (5 mmol, 0.5 ml) or piperazine (2.5 mmol, 0.22 g) in (95%) ethanol (30 ml) was heated to boiling, kept two days at room temperature, then for another four days in ice-chest. The products obtained were recrystallized from ethanol as yellow crystals (*cf.* Table II).

Compound	M.p. [°C]	Yield [%]	Formula (mol. wt.)	Analysis (%)		Found (calcd) N
				C	H	
13	280	48	C ₂₀ H ₁₉ NO ₃ (321.4)	74.50 (74.75)	5.41 (5.96)	4.31 (4.36)
14	270	55	C ₂₁ H ₂₁ NO ₂ (319.4)	78.35 (78.97)	6.38 (6.63)	4.28 (4.39)
15	202	60	C ₃₆ H ₃₀ N ₂ O ₄ (554.6)	77.58 (77.96)	5.20 (5.45)	5.01 (5.05)

Table II. Mannich bases **13–15**.

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