

## **CHAPTER 3**

### **EXPERIMENTAL**

#### **Instruments.**

##### **1. Infrared Spectrophotometers:**

- Perkin Elmer FT-IR model 1760x (The Scientific and Technological Research Equipment Center, Chulalongkorn University).
- Perkin Elmer model 283 (Faculty of Pharmaceutical Sciences Chulalongkorn University).
- Perkin Elmer 16 PC FT-IR (Pharmaceutical Technology Service Center, Chulalongkorn University).

##### **2 . Nuclear Magnetic Resonance Spectrophotometer:**

- Jeol JNM-A500 (500 Mhz) (The Scientific and Technological Research Equipment Center, Chulalongkorn University).

##### **3. Mass Spectrometer:**

- Kratos model Profile (Department of Science Service, Ministry of Science, Technology and Energy).

##### **4. Melting Point Apparatus:**

- Buchi capillary melting point apparatus (the thermometer is uncorrected).



## Chemicals.

Diethyl malonate (Fluka chemie AG).

Triethyl orthoformate (Fluka chemie AG).

Acetic anhydride (BDH Limited Poole England).

Phenylhydrazine (Fluka Chemie AG).

Ammonia Solution (25%) (Merck).

Tin (Fluka chemie AG).

All Solvents used were either B.P. or laboratory grade.

## Diethyl ethoxymethylenemalonate

A mixture of 160 g (1.0 mole) of diethyl malonate, 148 g (1.0 mole) of triethyl orthoformate, 204 g (2.0 moles) of acetic anhydride and 2-3 g of anhydrous zinc chloride were refluxed for 45 minutes. The mixture was then distilled at atmospheric pressure at 190°C. The residue was cooled, filtered and re-distilled under reduced pressure, the fraction was collected at b.p. 140 - 165°C (10 mmHg). The product was redistilled at 155-160°C (15 mmHg) (Duffin and Kendall, 1948). The yield of product was 120 g (55%), b.p. 155-160°C (15 mmHg).

IR (Figure 1, p. 61)	2980-2910	cm <sup>-1</sup>	(ν C-H)
(KBr Demountable cell)	1731	cm <sup>-1</sup>	(ν C=O, ester)
	1635	cm <sup>-1</sup>	(ν C=C)
	1290-1250	cm <sup>-1</sup>	(ν C-O, ester)
	1090	cm <sup>-1</sup>	(ν C-O, ester)



$^1\text{H}$ -NMR (Figure 2, p. 62)	1.28-1.45	ppm (9H, m)
(in $\text{CDCl}_3$ )	4.09-4.38	ppm (6H, m)
	7.60	ppm (1H, s)

### **Ethyl anilino - 3 - chloro - methylenemalonate**

A mixture of 3.89 g (30 mmole) of 3-chloroaniline and 6.48 g (30 mmole) of diethyl ethoxymethylenemalonate was refluxed in ethyl alcohol for 3 hours. After ethyl alcohol was evaporated, the residue was recrystallized from petroleum ether to give 7.70 g (86% yield) of the product, m.p.  $56^\circ\text{C}$ .

IR (Figure 3, p. 63)	3282	$\text{cm}^{-1}$ ( $\nu$ N-H)
(KBr Demountable cell)	3030-2850	$\text{cm}^{-1}$ ( $\nu$ C-H)
	1682	$\text{cm}^{-1}$ ( $\nu$ C=O, ester)
	1642	$\text{cm}^{-1}$ ( $\nu$ C=C)
	1615	$\text{cm}^{-1}$ ( $\delta$ N-H)
	1253	$\text{cm}^{-1}$ ( $\nu$ C-O, ester)
$^1\text{H}$ - NMR (Figure 4-5, p. 64-5)	1.34	ppm (3H, t, $J=7.2$ Hz)
(in $\text{CDCl}_3$ )	1.38	ppm (3H, t, $J=7.2$ Hz)
	4.26	ppm (2H, q, $J=7.2$ Hz)
	4.31	ppm (2H, q, $J=7.2$ Hz)
	7.00	ppm (1H, ddd, $J=8.1, 2.2, 0.8$ Hz)
	7.12	ppm (1H, ddd, $J=7.9, 1.8, 0.9$ Hz)
	7.15	ppm (1H, t, $J=1.9$ Hz)
	7.28	ppm (1H, t, $J=8.0$ Hz)



8.46 ppm (1H, d, J=13.4 Hz)

11.00 ppm (1H, d, J=13.5 Hz)

### **Ethyl anilino-3-nitro-methylenemalonate**

A mixture of 1.38 g (10 mmole) of 3-nitroaniline and 2.16 g (10 mmole) of diethyl ethoxymethylenemalonate was refluxed in ethyl alcohol for 16 hours. After ethyl alcohol was evaporated, the residue was recrystallized from ethyl acetate to give 2.68 g (87% yield) of the product, m.p. 81-82°C.

IR (Figure 6, p. 66) (KBr pellet)	3310	cm <sup>-1</sup> (ν N-H)
	3030-2850	cm <sup>-1</sup> (ν C-H)
	1696	cm <sup>-1</sup> (ν C=O, ester)
	1646	cm <sup>-1</sup> (ν C=C)
	1608	cm <sup>-1</sup> (δ N-H)
	1536,1350	cm <sup>-1</sup> (ν N-O)
<sup>1</sup> H-NMR (Figure 7-8, p. 67-8) (in CDCl <sub>3</sub> )	1261	cm <sup>-1</sup> (ν C-O)
	1.35 ppm	(3H, t, J=7.2 Hz)
	1.39 ppm	(3H, t, J=7.2 Hz)
	4.28 ppm	(2H, q, J=7.2 Hz)
	4.34 ppm	(2H, q, J=7.2 Hz)
	7.43 ppm	(1H, ddd, J=8.2, 2.3, 0.8 Hz)
	7.55 ppm	(1H, t, J=8.1 Hz)
	7.98 ppm	(1H, ddd, J=8.1, 2.1, 0.8 Hz)
	8.00 ppm	(1H, t, J=2.0 Hz)



8.50 ppm (1H, d, J=13.1 Hz)

11.17 ppm (1H, d, J=12.8 Hz)

**3-Carboethoxy - 7- chloro - 4 - hydroxyquinoline**

Ethyl anilino-3-chloro-methylenemalonate (3.0 g, 0.01 mole) was poured slowly through the top of an air condenser into 30 ml of boiling diphenyl ether and refluxed for 45 minutes. After the solution had cooled, the resulting precipitate was filtered and washed consecutively with benzene and diethyl ether. The solid was recrystallized from DMF to give 1.79 g (70% yield) of product, m.p. over 300°C.

IR (Figure 9, p. 69)	3150-2890	cm <sup>-1</sup> (ν C-H)
(KBr pellet)	1698	cm <sup>-1</sup> (ν C=O, ester)
	1621	cm <sup>-1</sup> (ν C=N)
	1464	cm <sup>-1</sup> (δ C-H)
	1378	cm <sup>-1</sup> (δ O-H)
	1354, 1197	cm <sup>-1</sup> (ν C-O, ester)

<sup>1</sup> H-NMR (Figure 10-11, p. 70-1)	1.28 ppm (3H, t, J=7.2 Hz)
(in DMSO-d <sub>6</sub> )	4.22 ppm (2H, q, J=7.2 Hz)
	7.42 ppm (1H, dd, J=8.7, 2.1 Hz)
	7.66 ppm (1H, d, J=2.1 Hz)
	8.14 ppm (1H, d, J=8.5 Hz)
	8.56 ppm (1H, s)
	12.24 ppm (broad, s)



### 3-Carboethoxy-7-nitro-4-hydroxyquinoline

Ethyl anilino-3-nitro-methylenemalonate (3.1 g, 0.01 mole) was poured slowly through the top of an air condenser into 35 ml of boiling diphenyl ether and refluxed for 45 minutes. After the solution had cooled, the resulting precipitate was filtered and washed consecutively with benzene and diphenyl ether. The solid was recrystallized from DMF to give 1.49 g (56% yield) of the product, m.p. over 300°C.

IR (Figure 12, p. 72)	3150-2890	cm <sup>-1</sup>	(ν C-H)
(KBr pellet)	1694	cm <sup>-1</sup>	(ν C=O, ester)
	1635	cm <sup>-1</sup>	(ν C=N)
	1567, 1356	cm <sup>-1</sup>	(ν N-O)
	1468	cm <sup>-1</sup>	(δ C-H)
	1381	cm <sup>-1</sup>	(δ O-H)
	1297, 1198	cm <sup>-1</sup>	(ν C-O, ester)
<sup>1</sup> H-NMR (Figure 13-14, p. 73-4)	1.29	ppm	(3H, t, J=7.2 Hz)
(in DMSO-d <sub>6</sub> )	4.24	ppm	(2H, q, J=7.2 Hz)
	8.12	ppm	(1H, dd, J=8.8, 2.1 Hz)
	8.36	ppm	(1H, d, J=8.8 Hz)
	8.50	ppm	(1H, d, J=2.1 Hz)
	8.71	ppm	(1H, s)
	12.57	ppm	(broad, s)



### 3-Carboethoxy-4,7-dichloroquinoline

A mixture of 1.19 g (4.68 mmole) of 3-carboethoxy-7-chloro-4-hydroxyquinoline and 5 ml of thionyl chloride was heated over a steam-bath for 15 minutes. The excess thionyl chloride was removed in vacuo then the crude residue was poured into 50 ml of ice to which had been added 12 ml of concentrated ammonia solution. The mass was stirred and kept cold until it became entirely granular, then it was filtered. The filtered cake was washed with water and dried. The solid was dissolved in chloroform and dried with anhydrous sodium sulfate. The solution was then filtered and chloroform removed on a rotary evaporator. The product was recrystallized from chloroform. The overall yield was 1.17 g (92% yield), m.p. 79-80°C.

IR (Figure 15, p. 75)	3074-2869	cm <sup>-1</sup>	(ν C-H)
(KBr pellet)	1728	cm <sup>-1</sup>	(ν C=O, ester)
	1582	cm <sup>-1</sup>	(ν C=C)
	1472	cm <sup>-1</sup>	(δ C-H)
	1228, 1197	cm <sup>-1</sup>	(ν C-O, ester)
<sup>1</sup> H-NMR (Figure 16-17, p. 76-7)	1.47	ppm	(3H, t, J=7.2 Hz)
(in CDCl <sub>3</sub> )	4.51	ppm	(2H, q, J=7.2 Hz)
	7.65	ppm	(1H, dd, J=9.1, 1.8 Hz)
	8.15	ppm	(1H, d, J = 1.8 Hz)
	8.35	ppm	(1H, d, J=8.9 Hz)
	9.21	ppm	(1H, s)



### 3-Carboethoxy-4-chloro-7-nitroquinoline

A mixture of 1.21 g (4.60 mmole) of 3-carboethoxy-7-nitro-4-hydroxyquinoline and 5 ml of thionyl chloride was heated over a steam-bath for 15 minutes. The excess thionyl chloride was removed in vacuo. The crude residue was then poured into 50 ml of ice to which had been added 12 ml of concentrated ammonia solution. The mass was stirred and kept cold until it became entirely granular after filtered. The filtered cake was washed with water and dried. The solid was dissolved in chloroform, dried with anhydrous sodium sulfate, filtered, and chloroform removed on a rotary evaporator. The product was recrystallized from chloroform. The overall yield was 1.18 g (90%), m.p. 149-150°C.

IR (Figure 18, p. 78)	3102-2865	cm <sup>-1</sup>	(ν C-H)
(KBr pellet)	1737	cm <sup>-1</sup>	(ν C=O, ester)
	1587	cm <sup>-1</sup>	(ν C=C)
	1533, 1350	cm <sup>-1</sup>	(ν N-O)
	1471	cm <sup>-1</sup>	(δ C-H)
	1235, 1210	cm <sup>-1</sup>	(ν C-O, ester)
<sup>1</sup> H-NMR (Figure 19-20, p 79-80)	1.49	ppm	(3H, t, J=7.2 Hz)
(in CDCl <sub>3</sub> )	4.54	ppm	(2H, q, J=7.2 Hz)
	8.46	ppm	(1H, dd, J=9.2, 1.2 Hz)
	8.59	ppm	(1H, d, J=9.4 Hz)
	9.03	ppm	(1H, broad, s)
	9.33	ppm	(1H, s)



### 7-Chloro-2-phenylpyrazolo-[4,3-c]-quinolin-3-one

A 0.207 g (0.767 mmole) of 3-carboethoxy-4,7-dichloroquinoline was heated with 0.166 g (1.534 mmole) of phenylhydrazine in xylene at 130-150°C for 3 hrs. After cooling, the resulting precipitate was removed by filtration, washed with water, methanol and chloroform, then dried in vacuo. The solid was crystallized from ethanol to give 0.16 g (70 % yield) of product, m.p. > 300°C.

IR (Figure 21, p. 81) 3060-2874  $\text{cm}^{-1}$  ( $\nu$  C-H)  
 (KBr pellet) 1616  $\text{cm}^{-1}$  ( $\nu$  C=O, amide)  
 1592  $\text{cm}^{-1}$  ( $\nu$  C=N)  
 1544  $\text{cm}^{-1}$  ( $\nu$  C=C)

$^1\text{H}$ -NMR (Figure 22-23, p. 82-3) 7.17 ppm (1H, t,  $J=7.3$  Hz)  
 (in DMSO- $d_6$ ) 7.43 ppm (2H, t,  $J=7.9$  Hz)  
 7.56 ppm (1H, dd  $J=8.6, 2.0$  Hz)  
 7.72 ppm (2H, d,  $J=2.1$  Hz)  
 8.18 ppm (2H, d,  $J=7.6$  Hz)  
 8.20 ppm (1H, d,  $J=8.6$  Hz)  
 8.75 ppm (1H, s)

$^{13}\text{C}$ -NMR (Figure 24, p. 84) :  $\delta$  106.68, 117.46, 118.66, 118.87,  
 124.04, 124.10, 165.52, 128.68,  
 134.24, 136.52, 139.93, 139.96,  
 142.33, 161.43 ppm

HH COSY spectrum (Figure 25-26, p. 85-6)

CH COSY spectrum (Figure 27-28, p. 87-8)



EIMS spectrum (Figure 29, p. 89) : 295(100%), 267(5.3%), 266(24.1%),  
 (m/e) 176(2.3%), 162(34.2%), 127(10.2%),  
 105(3.2%), 77(36.7%)

### 7-Nitro-2-phenylpyrazolo-[4,3-c]-quinolin-3-one

A 0.211 g (0.752 mmole) of 3-carboethoxy-4-chloro-7-nitroquinoline was heated with 0.163 g (1.507 mmole) of phenylhydrazine in xylene at 130-150°C for 17 hrs. After cooling, the resulting precipitate was removed by filtration, washed with water, methanol, and chloroform, then dried in vacuo. The solid was recrystallized from ethanol to give 0.092 g (40 % yield) of product, m.p. > 300°C.

IR (Figure 30, p. 90) 3032-2866  $\text{cm}^{-1}$  ( $\nu$  C-H)  
 (KBr pellet) 1628  $\text{cm}^{-1}$  ( $\nu$  C=O, amide)  
 1594  $\text{cm}^{-1}$  ( $\nu$  C=N)  
 1526,1350  $\text{cm}^{-1}$  ( $\nu$  N-O)  
 $^1\text{H-NMR}$  (Figure 31-32, p. 91-2) 7.20 ppm (1H, t,  $J=7.3$  Hz)  
 (in DMSO- $d_6$ ) 7.45 ppm (2H, t,  $J=7.9$  Hz)  
 8.18 ppm (2H, d,  $J=8.7$  Hz)  
 8.28 ppm (1H, dd,  $J=8.8, 2.1$  Hz)  
 8.40 ppm (1H, d,  $J=8.8$  Hz)  
 8.53 ppm (1H, d,  $J=2.4$  Hz)  
 8.89 ppm (1H, s)



$^{13}\text{C}$ -NMR (Figure 33, p. 93) :  $\delta$  106.93, 115.35, 118.84, 120.40,  
123.48, 123.64, 124.48, 128.74, 135.69,  
139.73, 141.18, 141.69, 147.48, 161.34  
ppm

HH COSY spectrum (Figure 34-35, p. 94-5)

CH COSY spectrum (Figure 36-37, p. 96-7)

EIMS spectrum (Figure 38, p. 98) : 306(3.1%), 277(0.5%), 276(1.9%),  
(m/e) 260(1.3%), 231(0.5%), 105(1.8%),  
77(4.8%)



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