第三節 實驗方法

(一) Ethyl 2-substituted anilino-4-oxo-4,5-dihydrofuran-3-carboxylate (1-23) 之合成

Ethyl 2-anilino-4-oxo-4,5-dihydrofuran-3-carboxylate (1) 之合成

取NaH (9.6 g，0.4 mole) (**預先以乾燥之** n-Hexane **洗去** NaH suspension **所含之** paraffin oil) **懸著於無水之** THF 60 ml **中後，緩慢滴入** diethyl malonate (61 ml，0.4 mole) **與** THF 60 ml **之混合溶液，當滴加完後冷卻至**10-12 **℃，再慢慢滴加** chloroacetyl chloride (15.9 ml，0.2 mole) **之** THF 200 ml **溶液，滴加完後保持低溫** (10-12 **℃**) **一小時隨後改用溫浴** (40-50 **℃**) **溫之約一小時，再冷卻至** 10-12 **℃。將**aniline (17.4 ml，0.1875 mole) **之** THF 80 ml **溶液滴入上述反應液中，於室溫攪拌一小時後，在水浴上加熱一小時，減壓濃縮去除大部份之** THF **後，倒入冰水，再以** $CHCl_3$ **萃取多次，其萃取液經水洗後，以無水** $MgSO_4$ **乾燥，濃縮後置於室溫下令其結晶，收集結晶用乙醇再結晶，收集淡黃色針狀結晶為化合物 1** (23.7 g，51.2 %); mp: 142-143 **℃。光譜數據如下**: MS *m/z*: 247; IR (KBr) cm^{-1}: 3209.4 (NH), 1701.4 (C_3=O), 1664.0 (-C=OOCH_2CH_3); UV λ_{max} nm (MeOH) (log ε): 273 (4.49); $C_{13}H_{13}NO_4$, calcd.(found) (%), C: 63.15 (63.10), H: 5.30 (5.26); ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.2 Hz, -COO$CH_2C\underline{H}_3$), 4.22 (2H, q, J=7.2 Hz, -COO-C$\underline{H}_2CH_3$), 4.54 (2H, s, H-5), 7.11-7.28 (5H, m, Ar-H), 10.15 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ : 14.19 (-COO$CH_2\underline{C}H_3$), 60.19 (-COO$\underline{C}H_2CH_3$), 75.13 (C-5), 87.31 (C-3), 121.12 (C-6′, C-2′), 125.81 (C-4′), 129.14 (C-3′, C-5′), 134.55 (C-1′), 165.20 (C-2), 177.31 (C-$\underline{C}OOCH_2CH_3$), 188.10 (C-4).

Ethyl 2-(3'-methylanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (2)之合成

比照化合物 1 之製造方法過程而以 *m*-toluidine (20 ml，0.1875 mole)**替代** aniline **進行之，得到淡黃色針狀結晶為化合物 2** (26.2 g，53.6 %)，mp：113-114 **℃。光譜數據如下**: MS *m/z*: 261; IR (KBr) cm^{-1}: 3252.2 (NH), 1705.2 (C_3=O), 1655.0 (-C=OOCH_2CH_3); UV λ_{max} nm (MeOH) (log ε): 275 (4.40); $C_{14}H_{15}NO_4$, calcd.(found) (%), C: 64.35 (64.30), H: 5.78 (5.70); ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.2 Hz, -COO$CH_2C\underline{H}_3$), 2.31 (3H, s, $C_{3'}$-C$\underline{H}_3$), 4.31 (2H, q, J=7.2 Hz, -COO -C$\underline{H}_2CH_3$), 4.61 (2H, s, H-5), 6.97-7.22 (4H, m, Ar-H), 10.17 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 14.23 (-COO$CH_2\underline{C}H_3$), 21.13 (C3′-$\underline{C}H_3$), 60.26 (-COO$\underline{C}H_2CH_3$), 75.17 (C-5), 87.31 (C-3), 118.23 (C-6′), 121.77 (C-2′), 126.70 (C-4′), 129.00 (C-5′), 134.47 (C-3′), 139.29 (C-1′), 165.29 (C-2), 177.34 (-$\underline{C}OOCH_2CH_3$), 188.16(C-4).

Ethyl 2-(3'-ethylanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (3)之合成

比照化合物 1 之製造方法過程，而以 *m*-ethylaniline (22 ml，0.1875 mole)**替代** aniline **進行之，得到淡黃色針狀結晶為化合物 3** (29.0 g，56.8 %)，mp：122-123 **℃。光譜數據如下**: MS *m/z*: 275; IR (KBr) cm^{-1}: 3248.3 (NH), 1705.2

(C_3=O), 1658.9 (-C=OOCH_2CH_3); UV λ_{max} nm (MeOH) (log ε): 275 (4.43); $C_{15}H_{17}NO_4$, calcd.(found) (%), C: 65.44 (65.34), H: 6.22 (6.18); ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.6 Hz, $C_{3'}$-CH$_2$C$\underline{H}_3$), 1.36 (2H, q, J=7.2 Hz, -COOC$\underline{H}_2$CH$_3$), 2.64 (3H, t, J=7.6 Hz, -COOCH$_2$C$\underline{H}_3$), 4.35 (2H, q, J=7.2 Hz, $C_{3'}$- C$\underline{H}_2$CH$_3$), 4.65 (2H, s, H-5), 7.03-7.28 (4H, m, Ar-H), 10.22 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 14.25 (-COO- CH$_2$C$\underline{H}_3$), 15.11 ($C_{3'}$-CH$_2$C$\underline{H}_3$), 28.49 ($C_{3'}$-C$\underline{H}_2$CH$_3$), 60.31 (-COOC$\underline{H}_2$CH$_3$), 75.20 (C-5), 87.33 (C-3), 118.50 (C-6′), 120.70 (C-2′), 125.57 (C-4′), 129.12 (C-5′), 134.55 (C-1′), 145.70 (C-3′), 165.36 (C-2), 177.38 (C-COOC$_2$H$_5$), 188.17 (C-4).

Ethyl 2-(3'-methoxyanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (4) 之合成

比照化合物 1 之製造方法過程，而以 *m*-anisidine (20 ml，0.1875 mole)**替代** aniline **進行之，得到淡黃色針狀結晶為化合物 4** (28.7 g，55.2 %)，mp：142-143**℃。光譜數據如下：**MS *m/z*: 277; IR (KBr) cm^{-1}: 3275.3 (NH), 1697.5 (C_3=O), 1662.7 (-C=OOCH_2CH_3); UV λ_{max} nm (MeOH) (log ε): 277 (4.20); $C_{14}H_{15}NO_5$, calcd.(found) (%), C: 60.64 (60.40), H: 5.45 (5.37); ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7.1 Hz, -COOCH$_2$C$\underline{H}_3$), 3.73 (3H, s, C_3′-OC$\underline{H}_3$), 4.27 (2H, q, J=7.1Hz,-COOC$\underline{H}_2$CH$_3$), 4.58 (2H, s, H-5), 6.70 (1H, d, J=8.0 Hz, H-6′), 6.84-6.88 (2H, m, H-2′, H-4′), 7.25 (1H, t, J=8.4 Hz, H-5′), 10.17 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ : 14.20 (-COOCH$_2$C$\underline{H}_3$), 55.14 ($C_{3'}$-OC$\underline{H}_3$), 60.25 (-COOC$\underline{H}_2$CH$_3$), 75.20 (C-5), 87.39 (C-3), 107.18 (C-2′), 111.09 (C-4′), 113.25 (C-6′), 129.95 (C-5′), 135.63 (C-1′), 160.06 (C-3′), 165.26 (C-2), 177.36 (C-3), 188.08 (C-4).

Ethyl 2-(3'-ethoxyanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (5)之合成

比照化合物 1 之製造方法過程，而以 *m*-phenetidine (26 ml，0.1875 mole) **替代** aniline **進行之，得到針狀淡黃色結晶為化合物 5** (33.7 g，61.8 %)，mp：116-117 **℃。光譜數據如下：**MS *m/z*: 291; IR (KBr) cm^{-1}: 3169.2 (NH), 1701.3 (C_3=O), 1658.9 (-C=OOCH_2CH_3); UV λ_{max} nm (MeOH) (log ε): 276 (4.47); $C_{15}H_{17}NO_5$, calcd.(found) (%), C: 61.84 (61.28), H: 5.88 (5.67); ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.2 Hz, -COOCH$_2$C$\underline{H}_3$), 1.38 (3H, t, J=7.0 Hz, $C_{3'}$-OCH$_2$C$\underline{H}_3$), 4.00 (2H, q, J=7.0 Hz, $C_{3'}$-OC$\underline{H}_2$CH$_3$), 4.33 (2H, q, J=7.2 Hz, -COOC$\underline{H}_2$CH$_3$), 4.64 (2H, s, H-5), 6.72 (1H, dd, J=8.2, 2.1 Hz, H-6′), 6.86-6.91 (2H, m, H-2′, H-4′), 7.28 (1H, dd, J=8.2, 2.1 Hz, H-5′), 10.22 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 14.25 (-COOCH$_2$C$\underline{H}_3$), 14.46 ($C_{3'}$-OCH$_2$C$\underline{H}_3$), 60.33 (-COOC$\underline{H}_2$CH$_3$), 63.46 ($C_{3'}$-OC$\underline{H}_2$CH$_3$), 75.24 (C-5), 87.43 (C-3), 107.72 (C-2′), 111.72 (C-4′), 113.17 (C-6′), 129.97 (C-5′), 135.60 (C-1′), 159.48 (C-3′), 165.33 (C-2), 177.40 (C-C$\underline{O}$OC$_2$H$_5$), 188.13 (C-4).

Ethyl 2-(3'-chloroanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (6)之合成

比照化合物 1 之製造方法過程，而以 *m*-chloroaniline (24 ml，0.1875 mole)**替代**aniline**進行之，得到白色針狀結晶為化合物 6** (27.4g，52.0 %)，mp：115-116 **℃。** MS *m/z*: 281; IR (KBr) cm^{-1}: 3171.2 (NH), 1697.5 (C_3=O),1662.7 (-

C=OOCH$_2$CH$_3$); UV λ_{max} nm (MeOH) (log ε): 277 (4.50); $C_{13}H_{12}ClNO_4$, calcd.(found) (%), C: 55.43 (55.08), H: 4.29 (4.13); ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7.1Hz, -COOCH$_2$C<u>H</u>$_3$), 4.36 (2H, q, J=7.1Hz, -COOC<u>H</u>$_2$CH$_3$) 4.70 (2H, s, H-5), 6.89 (1H, m, H-4′), 7.17-7.32 (3H, m, H-4′, H-5′, H-6′), 7.45 (1H, d, J=2.0 Hz, H-2′), 10.32 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 14.23 (-COOCH$_2$<u>C</u>H$_3$), 60.53 (-COO<u>C</u>H$_2$CH$_3$), 75.38 (C-5), 87.77 (C-3), 119.08 (C-6′), 121.13 (C-2′), 125.89 (C-4′), 130.26 (C-5′), 134.95 (C-3′), 135.75 (C-1′), 165.32 (C-2), 177.58 (C-<u>C</u>OOC$_2$H$_5$), 188.09 (C-4).

Ethyl 2-(3'-fluoroanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (7)之合成

比照化合物1之製造方法過程，而以 *m*-fluoroaniline(21ml，0.1875mole)**替代** aniline**進行之，得到白色針狀結晶為化合物 7** (26.5g，53.4%)，mp：136-137 **℃。** MS *m/z*: 265; IR (KBr) cm^{-1}: 3274.1 (NH), 1701.3 (C_3=O), 1655.0 (-C=OOCH$_2$CH$_3$); UV λ_{max} nm (MeOH) (log ε): 280 (4.46); $C_{13}H_{12}FNO_4$, calcd.(found) (%), C: 58.86 (58.40), H: 4.56 (4.48); ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.1Hz, -COOCH$_2$C<u>H</u>$_3$), 4.32 (2H, q, J=7.1Hz, -COOC<u>H</u>$_2$CH$_3$), 4.66 (2H, s, H-5), 6.89 (1H, m, H-4′), 7.11 (1H, m, H-6′), 7.17 (1H, m, J= 10.1, 2.2 Hz, H-2′), 7.31 (1H, m, J=8.2, 6.3 Hz, H-5′), 10.34 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 14.19 (-COOCH$_2$<u>C</u>H$_3$), 60.46 (-COO<u>C</u>H$_2$CH$_3$), 75.34 (C-5), 87.71 (C-3), 108.47 (d,J=25.0 Hz, C-2′), 112.60 (d, J=21.0 Hz, C-4′), 116.48 (C-6′), 130.50 (d, J=9.1 Hz, C-5′), 136.04 (d, J=10.5 Hz, C-1′), 160.23 (C-3′), 165.27 (C-2), 177.53 (C-<u>C</u>OOC$_2$H$_5$), 188.09 (C-4).

Ethyl 2-(3'-bromoanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (8)之合成

比照化合物1之製造方法過程，而以 *m*-bromoaniline (26ml，0.1875mole)**替代** aniline**進行之，得到針狀淡黃色結晶為化合物 8** (33.7g，61.8%)，mp：116-117 **℃。 光譜數據如下：**MS *m/z*: M^+ 325, (M+2) M^+ 327; IR (KBr) cm^{-1}: 3164.2 (NH), 1670.0 (C_3=O), 1624.1 (-C=OOCH$_2$CH$_3$); UV λ_{max} nm (MeOH) (log ε): 277.6 (4.74); $C_{13}H_{12}BrNO_4$, calcd.(found) (%), C: 47.87 (47.29), H: 3.70 (3.58); ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7.2Hz, -COOCH$_2$C<u>H</u>$_3$), 4.35 (2H,q, J=7.2Hz,-COOC<u>H</u>$_2$CH$_3$), 4.69 (2H, s, H-5), 7.23-7.36 (3H, m, H-4′, H-5′, H-6′), 7.59 (1H, d, J=2.2Hz, H-2′), 10.30 (1H, s,NH); ^{13}C-NMR ($CDCl_3$) δ: 14.23 (-COOCH$_2$<u>C</u>H$_3$), 60.53 (-COO<u>C</u>H$_2$CH$_3$), 75.39 (C-5), 87.77 (C-3), 119.56 (C-6′), 122.79 (C-3′), 123.96 (C-2′), 128.81 (C-5′), 130.51 (C-4′), 135.87 (C-1′), 165.31 (C-2), 177.56 (C-COOC$_2$H$_5$), 188.07 (C-4).

Ethyl 2-(4'-methylanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (9)之合成

比照化合物1之製造方法過程，而以*p*-toluidine (20ml，0.1875mole)**替代** aniline**進行之，得到黃色針狀結晶為化合物 9** (28.6g，58.4%)，mp：126-127 **℃。** MS *m/z*: 261; IR (KBr) cm^{-1}: 3273.6 (NH), 1701.3 (C_3=O), 1658.9 (-C=OOCH$_2$CH$_3$); UV λ_{max} nm (MeOH) (log ε): 275 (4.44); $C_{14}H_{15}NO_4$, calcd.(found) (%), C: 64.35 (63.79), H: 5.78 (5.37);^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.1Hz, -COOCH$_2$C<u>H</u>$_3$), 2.29 (3H, s, $C_{4'}$-C<u>H</u>$_3$), 4.31 (2H, q, J=7.1Hz, -COOC<u>H</u>$_2$CH$_3$), 4.60 (2H, s, H-5), 7.10-7.22 (4H, m, Ar-H), 10.12 (1H, s, NH) ; ^{13}C-NMR ($CDCl_3$) δ: 14.29 (-COOCH$_2$<u>C</u>H$_3$), 20.69 ($C_{4'}$-CH$_3$), 60.34 (-COO<u>C</u>H$_2$CH$_3$), 75.17 (C-5), 87.96

(C-3), 121.35 (C-2′, C-6′), 129.78 (C-3′, C-5′), 131.95 (C-4′), 136.03(C-1′), 165.40(C-2′), 177.36 (C-$COOC_2H_5$), 188.19 (C-4).

Ethyl 2-(4'-ethylanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (10)之合成

比照化合物1之製造方法過程，而以*p*-ethylaniline (22ml，0.1875mole)**替代**aniline**進行之，得到淡黃色針狀結晶為化合物 10** (31.4g，60.8%)，mp：108-111 **℃。光譜數據如下：**MS *m/z*: 275; IR (KBr) cm^{-1}: 3205.9 (NH), 1704.4 (C_3=O), 1674.3 (-C=OOCH_2CH_3); UV λ_{max} nm (MeOH) (log ε): 276 (4.45); $C_{15}H_{17}NO_4$, calcd.(found) (%), C: 65.44 (64.50), H: 6.22 (5.98); ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, t, J=8.0 Hz, C4′-$CH_2C\underline{H}_3$), 1.36 (3H, t, J=7.0 Hz, -$COOCH_2C\underline{H}_3$), 2.62 (2H, q, J=8.0 Hz, $C_{4'}$-$C\underline{H}_2CH_3$), 4.34 (2H, q, J=7.0 Hz, -$COOC\underline{H}_2CH_3$), 4.63 (2H, s, H-5), 7.16-7.28 (4H, m, Ar-H), 10.17 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 14.26 (-$COOCH_2\underline{C}H_3$), 15.20 ($C_{4'}$-$CH_2C\underline{H}_3$), 28.05 ($C_{4'}$-$\underline{C}H_2CH_3$), 60.27 (-$COO\underline{C}H_2CH_3$), 75.15 (C-5), 87.33 (C-3), 121.39 (C-2′, C-6′), 128.56 (C-3′, C-5′), 132.10 (C-1′), 142.30 (C-4′), 165.34 (C-2), 177.31 (C-$COOC_2H_5$), 188.14 (C-4).

Ethyl 2-(4'-methoxyanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (11) 之合成

比照化合物1之製造方法過程，而以*p*-anisidine (20ml，0.1875mole)**替代**aniline**進行之，得到淡黃色針狀結晶為化合物11** (30.4g，58.6%)，mp：138-139 **℃。光譜數據如下：**MS *m/z*: 277; IR (KBr) cm^{-1}: 3283.1(NH), 1697.5 (C_3=O), 1658.9 (-C=OOCH_2CH_3); UV λ_{max} nm (MeOH) (log ε): 277 (4.30); $C_{14}H_{15}NO_5$, calcd.(found) (%), C: 60.64 (58.90), H: 5.45 (5.35); ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.1Hz,-$COOCH_2C\underline{H}_3$), 3.69(3H,s,$C_{4'}$-$OC\underline{H}_3$), 4.22 (2H, q, J=7.1Hz, -$COOC\underline{H}_2CH_3$), 4.51 (2H, s, H-5), 6.89 (2H, dd, J=9.0, 2.2Hz, H-3′, H-5′), 7.17 (2H, dd, J=9.0, 2.2Hz, H-2′, H-6′), 9.98 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 14.29 (-$COOCH_2\underline{C}H_3$), 55.27 ($C_{4'}$-$O\underline{C}H_3$), 60.27 (-$COO\underline{C}H_2CH_3$), 75.11 (C-5), 87.08 (C-3), 114.33 (C-2′, C-6′), 123.22 (C-3′, C-5′), 127.28 (C-1′), 157.67 (C-4′), 165.35 (C-2), 177.21 (C-$COOC_2H_5$), 188.14 (C-4).

Ethyl 2-(4'-ethoxyanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (12)之合成

比照化合物1之製造方法過程，而以*p*-phenetidine (26ml，0.1875mole)**替代**aniline**進行之，得到白色絮狀結晶為化合物 12** (34g，62.3%)，mp：148-149**℃。光譜數據如下：**MS *m/z*: 291; IR (KBr) cm^{-1}: 3186.6 (NH), 1685.9 (C_3=O), 1658.9 (-C=OOCH_2CH_3); UV λ_{max} nm (MeOH) (log ε): 278 (4.35); $C_{15}H_{17}NO_5$, calcd.(found) (%), C: 61.84 (60.45), H: 5.88 (5.60); ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7.0Hz, -$COOCH_2C\underline{H}_3$), 1.42 (3H, t, J=6.9Hz, C_6-$OCH_2C\underline{H}_3$), 4.25 (2H, q, J=6.9Hz, $C_{4'}$-$OC\underline{H}_2CH_3$) 4.37 (2H, q, J=7.0Hz, -$COOC\underline{H}_2CH_3$), 4.64 (2H, s, H-5), 6.90 (2H, m, H-2′, H-6′), 7.26 (2H, m, H-3′, H-5′), 10.08 (1H, s, NH) ^{13}C-NMR ($CDCl_3$) δ: 14.49 (-$COOCH_2\underline{C}H_3$), 14.71($C_{4'}$-$OCH_2\underline{C}H_3$), 60.48 (-$COO\underline{C}H_2CH_3$), 63.74 ($C_{4'}$-$O\underline{C}H_2CH_3$), 87.27 (C-3), 75.31 (C-5), 115.07 (C-2′, C-6′), 123.39 (C-3′, C-5′), 127.33 (C-1′), 157.28 (C-4′), 165.58 (C-2), 177.41(C-$COOC_2H_5$), 188.32 (C-4).

Ethyl 2-(4'-chloroanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (13) 之合成

比照化合物1之製造方法過程，而以*p*-chloroaniline(24ml，0.1875mole)**替代**aniline**進行之，得到黃色針狀結晶為化合物 13** (29.0g，54.9%)，mp：167-168 **℃。光譜數據如下：**MS *m/z*: 281; IR (KBr) cm^{-1}: 3164.1 (NH), 1693.6 (C_3=O), 1658.9 (-C=OOCH_2CH_3); UV λ_{max} nm (MeOH) (log ε): 277 (4.64); $C_{13}H_{12}ClNO_4$, calcd.(found) (%), C: 55.43 (54.26), H: 4.29 (4.17); ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.1Hz, -COO$CH_2C\underline{H}_3$), 4.20 (2H, q, J=7.1Hz, -COO$C\underline{H}_2CH_3$), 4.67 (2H, s, H-5), 7.45-7.50 (4H, m, Ar-H), 10.29 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 14.24 (-COO-$CH_2\underline{C}H_3$), 60.51 (-COO$\underline{C}H_2CH_3$), 75.31 (C-5), 87.64 (C-3), 122.40 (C-2′, C-6′), 129.38 (C-3′,C-5′), 131.38 (C-4′), 133.20 (C-1′), 165.38 (C-2), 177.50 (C-$COOC_2H_5$), 188.06 (C-4).

Ethyl 2-(4'-fluoroanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (14) 之合成

比照化合物1之製造方法過程，而以*p*-fluoroaniline (21ml，0.1875mole)**替代**aniline**進行之，得到黃色針狀結晶為化合物14** (27.5g，55.4%)，mp：154-155 **℃。光譜數據如下：**MS *m/z*: 265; IR (KBr) cm^{-1}: 3136.5 (NH), 1693.6 (C_3=O), 1662.7 (-C=OOCH_2CH_3); UV λ_{max} nm (MeOH) (log ε): 267 (4.35); $C_{13}H_{12}FNO_4$, calcd.(found) (%), C: 58.86 (57.93), H: 4.56 (4.38); ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J=7.1Hz；-COO$CH_2C\underline{H}_3$), 4.32 (2H, q, J=7.1Hz, -COO$C\underline{H}_2CH_3$), 4.63 (2H, s, H-5), 7.01-7.10 (2H, m, H-3′, H-5′), 7.29-7.35 (2H, m, H-2′, H-6′), 10.18 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 14.22 (-COO$CH_2\underline{C}H_3$), 60.37 (-COO$\underline{C}H_2CH_3$), 75.19 (C-5), 87.34 (C-3), 116.08 (C-3′, C-5′), 123.31 (d,J=8.2 Hz, C-2′, C-6′), 130.51 (C-1′), 160.29 (d, J= 245.0 Hz, C-4′), 165.31 (C-2), 177.42 (C-$COOC_2H_5$), 188.07 (C-4).

Ethyl 2-(4'-bromoanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (15) 之合成

比照化合物1之製造方法過程，而以*p*-bromoaniline (32.3g，0.1875mole)**替代**aniline**進行之，得到黃色針狀結晶為化合物 15** (35.4g，58.1%)，mp: 173-175 **℃。光譜數據如下：**MS *m/z*:M^+325, $(M+2)^+$ 327 ; IR (KBr) cm^{-1}: 3170.0 (NH), 1663.7 (C_3=O), 1617.6 (-C=OOCH_2CH_3); UV λ_{max} nm (MeOH) (log ε): 280 (4.72); $C_{13}H_{12}BrNO_4$, calcd.(found) (%), C: 47.87 (46.51), H: 3.70 (3.43);^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t, J=7.2 Hz, -COO$CH_2C\underline{H}_3$), 4.34 (2H, q, J=7.2 Hz, -COO$C\underline{H}_2CH_3$), 4.67 (2H, s, H-5), 7.25 (2H, d,J=8.8Hz, H-2′, H-6′), 7.49 (2H, d, J=8.8Hz, H-3′, H-5′), 10.27(1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 14.24 (-COO$CH_2\underline{C}H_3$), 60.49 (-COO$\underline{C}H_2CH_3$), 75.31 (C-5), 87.66 (C-3), 119.00 (C-4′), 122.63 (C-2′, C-6′), 132.31 (C-3′, C-5′), 133.71 (C-1′), 165.34 (C-2), 177.44 (C_3-$COOC_2H_5$), 188.04 (C-4).

Ethyl 2-(2',4'-dimethoxyanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (16) 之合成

比照化合物1之製造方法過程，而以2,4-dimethoxyaniline (21ml，0.1875mole) **替代**aniline**進行之，得到黃色針狀結晶為化合物 16** (30.1g，52.3%)，mp：154-155**℃。光譜數據如下：**MS *m/z*: 307; IR (KBr) cm^{-1}: 3264.6 (NH), 1751.5 (C_3=O), 1643.1 (-C=OOCH_2CH_3); UV λ_{max} nm (MeOH) (log ε): 280 (4.75); $C_{15}H_{17}NO_6$, calcd.(found) (%), C: 58.62 (57.63), H: 5.57 (5.51); ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t,

J=7.2 Hz, -COOCH$_2$C<u>H</u>$_3$), 3.77 (3H, s, -C$_{2'}$OCH$_3$), 3.87 (3H, s, 4′), 4.33 (2H, q, J=7.2 Hz, -COOC<u>H</u>$_2$CH$_3$), 4.61 (2H, s, H-2), 6.42 (1H, dd, J=8.8, 2.6 Hz, H-5′), 6.49 (1H, d, J=2.6Hz, H-3′), 7.54 (1H, d, J=8.8 Hz, H-6′), 10.34 (1H, s, NH); ^{13}C-NMR (CDCl$_3$) δ: 14.28 (-COOCH$_2$<u>C</u>H$_3$), 55.30 (C$_{4'}$-O<u>C</u>H$_3$), 55.82 (C$_{2'}$-OCH$_3$), 60.04 (-COO<u>C</u>H$_2$CH$_3$), 75.08 (C-5), 87.41 (C-3), 98.73 (C-3′), 103.84(C-5′), 117.73 (C-1′), 121.63 (C-6′), 150.73 (C-2′), 158.03(C-4′), 164.93 (C-2), 176.61 (C-COOC$_2$H$_5$), 188.18 (C-4).

Ethyl 2-(3',4'-dimethoxyanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (17) 之合成

比照化合物1之製造方法過程，而以3,4-dimethoxyaniline (28.7g，0.1875mole) **替代**aniline**進行之，得到黃色針狀結晶為化合物 17** (29.3g，51.0%)，mp：154-155**℃。光譜數據如下：**MS *m/z*: 307; IR (KBr) cm^{-1}: 3264.6 (NH), 1751.5 (C$_3$=O), 1643.1 (-C=OOCH$_2$CH$_3$); UV λ$_{max}$ nm (MeOH) (log ε): 280 (4.65); C$_{15}$H$_{17}$NO$_6$, calcd.(found) (%), C: 58.62 (56.81), H: 5.57 (5.49); ^{1}H-NMR (CDCl$_3$) δ: 1.32 (3H, t, J=7.0 Hz, -COOCH$_2$C<u>H</u>$_3$), 3.82 (6H, s, -C$_{3'}$OCH$_3$, -C$_{4'}$OCH$_3$), 4.30 (2H, q, J=7.0 Hz, -COOC<u>H</u>$_2$CH$_3$), 4.60 (2H, s, H-5), 6.77-6.91 (3H, m, Ar-H), 10.08 (1H, s, NH); ^{13}C-NMR (CDCl$_3$) δ: 14.30 (-COOCH$_2$<u>C</u>H$_3$), 55.89 (C$_{3'}$O<u>C</u>H$_3$, C$_{4'}$OCH$_3$), 60.32 (-COO<u>C</u>H$_2$CH$_3$), 75.22 (C-5), 87.14 (C-3), 106.01 (C-2′), 111.18 (C-6′), 113.96 (C-5′), 127.60 (C-1′), 147.29 (C-3′), 149.18 (C-4′), 165.43 (C-2), 177.23 (C-<u>C</u>OOC$_2$H$_5$), 188.06 (C-4).

Ethyl 2-(3',4'-dichloroanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (18) 之合成

比照化合物1之製造方法過程，而以3,4-dichloroaniline(30.3g，0.1875mole)**替代**aniline**進行之，得到黃色針狀結晶為化合物 18** (29.6g，50.0%)，mp：190-191**℃。光譜數據如下：**MS *m/z*: M$^+$ 314.9, (M+2)$^+$ 317.0, (M+4)$^+$ 319.0; IR (KBr) cm^{-1}: 3271.5 (NH), 1751.5 (C$_3$=O), 1697.5 (-C=OOCH$_2$CH$_3$); UV λ$_{max}$ nm (MeOH) (log ε): 281 (4.57); C$_{13}$H$_{11}$Cl$_2$NO$_4$, calcd.(found) (%), C: 49.39 (48.97), H: 3.50 (3.35); ^{1}H-NMR (CDCl$_3$) δ: 1.39 (3H, t, J=7.0 Hz, -COOCH$_2$C<u>H</u>$_3$), 4.38 (2H, q, J=7.0 Hz, -COOC<u>H</u>$_2$CH$_3$), 4.72 (2H, s, H-5), 7.21 (1H, dd, J=8.8, 2.6 Hz, H-6′), 7.46 (1H, d, J=8.8, Hz, H-5′), 7.57 (1H, d, J=2.6 Hz, H-2′), 10.36 (1H, s, NH); ^{13}C-NMR (CDCl$_3$) δ: 14.45 (-COOCH$_2$<u>C</u>H$_3$), 60.88 (-COO<u>C</u>H$_2$CH$_3$), 75.69 (C-5), 88.16 (C-3), 120.42 (C-6′), 122.91 (C-2′), 129.80 (C-1′), 131.08 (C-5′), 133.50 (C-4′), 134.28 (C-3′), 165.57 (C-2), 177.80 (C-COOC$_2$H$_5$), 188.18 (C-4).

Ethyl 2-(3',4'-dimethylanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (19) 之合成

比照化合物1之製造方法過程，而以3,4-dimethylaniline (22.7g，0.1875mole) **替代**aniline**進行之，得到黃色針狀結晶為化合物 19** (29.1g，56.5%)，mp：114-115**℃。光譜數據如下：**MS *m/z*: 275.0; IR (KBr) cm^{-1}: 3249.1 (NH), 1767.3 (C$_3$=O), 1613.0 (-C=OOCH$_2$CH$_3$); UV λ$_{max}$ nm (MeOH) (log ε): 227 (4.60); C$_{15}$H$_{17}$NO$_4$, calcd.(found) (%), C: 65.44 (63.98), H: 6.22 (5.87); ^{1}H-NMR (CDCl$_3$) δ: 1.34 (3H, t, J=7.2 Hz, -COOCH$_2$C<u>H</u>$_3$), 2.21 (3H, s, C$_{4'}$-CH$_3$), 2.29 (3H, s, C$_{3'}$-CH$_3$), 4.32 (2H, q, J=7.2 Hz, -COOC<u>H</u>$_2$CH$_3$), 4.61 (2H, s, H-5), 7.08 (3H, m, H-2′, H-5′, H-6′), 10.14

(1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 14.25 (-$COOCH_2\underline{C}H_3$), 18.97 ($C_{4'}$-$\underline{C}H_3$), 19.59 ($C_{3'}$-CH_3), 60.22 (-$COO\underline{C}H_2CH_3$), 75.13 (C-5), 87.16 (C-3), 118.72 (C-6′), 122.51 (C-2′), 130.14 (C-5′), 132.14 (C-4′), 134.65 (C-3′), 137.67 (C-1′), 165.30 (C-2), 177.22 (C- $COOC_2H_5$), 188.17 (C-4).

Ethyl 2-(3',4'-methylenedioxy)-4-oxo-4,5-dihydrofuran-3-carboxylate (20) 之合成

比照化合物1之製造方法過程，而以3,4-methylenedioxyaniline (25.7g，0.1875mole)**替代**aniline**進行之，得到黃色針狀結晶為化合物20** (26.0g，47.8%)，mp：154-155**℃。光譜數據如下：**MS *m/z*: 291.0; IR (KBr) cm^{-1}: 3264.6 (NH), 1759.6 (C_3=O), 1674.7 (-C=$OOCH_2CH_3$); UV λ_{max} nm (MeOH) (log ε): 278 (4.46); $C_{14}H_{13}NO_6$, calcd.(found) (%), C: 57.73 (56.50), H: 4.49 (4.35); ^{1}H-NMR ($CDCl_3$)δ: 1.37(3H, t, J=7.2 Hz, -$COOCH_2C\underline{H}_3$), 4.35(2H, q, J=7.2 Hz, -$COOC\underline{H}_2CH_3$), 4.64 (2H, s, H-5), 5.99 (2H, s, -OCH_2O-), 6.77 (2H, d, J=1.9 Hz, H-5′, H-6′), 6.92 (1H, d, J=1.3 Hz, H-2′), 10.10 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 14.28 (-$COOCH_2\underline{C}H_3$), 60.35 (-$COO\underline{C}H_2CH_3$), 75.18 (C-5), 87.18 (C-3), 101.58 (-OCH_2O-), 103.59 (C-2′), 108.20 (C-5′), 115.12 (C-6′), 128.33 (C-1′), 145.75 (C-4′), 148.04 (C-3′), 165.37 (C-2), 177.24 (C-$COOC_2H_5$), 188.09 (C-4).

Ethyl 2-(2¢-bromoanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate（21）之合成

比照化合物 1 之製造方法過程，而以 2-bromoaniline (32.3g，0.1875mole)**替代** aniline **進行之，得到黃色針狀結晶為化合物 21** (31.3g，51.3%)，mp：133-134**℃。光譜數據如下：**MS *m/z*: M^+ 325, $(M+2)^+$ 327; IR (KBr): 3137.8 (NH): 1768.9 (C_3-COOEt), 1676.8 (-C=$OOCH_2CH_3$); UV λ_{max} nm (MeOH) (log ε): 278.8 (4.40); $C_{13}H_{12}BrNO_4$, calcd.(found) (%), C: 47.87 (46.51), H: 3.70 (3.59);^{1}H-NMR ($CDCl_3$) δ : 1.26 (3H, t, J=7.2Hz, CH_2-$C\underline{H}_3$), 4.23 (2H, q, J=7.2Hz, $C\underline{H}_2$-CH_3), 4.71 (2H, s, H-5), 7.20-7.28 (1H, m, H-5′), 7.42-7.50 (2H, m, H-4′, H-6′), 7.69-7.78 (1H, m, H-3), 10.46 (1H, s, N$\underline{H}$); ^{13}C-NMR ($CDCl_3$) δ : 14.64 ($CH_2\underline{C}H_3$), 59.61 ($\underline{C}H_2CH_3$), 75.63 (C_5), 87.40 (C_3), 117.57 ($C_{2'}$), 125.75 ($C_{6'}$), 128.40 ($C_{4'}$), 128.84 ($C_{5'}$), 133.20 ($C_{3'}$), 133.86 ($C_{1'}$), 164.01 ($\underline{C}OOCH_2CH_3$), 177.30 (C-2′), 188.95 (C_4).

Ethyl 2-(3',5'-dichloroanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (22) 之合成

比照化合物1之製造方法過程，而以3,5-dichloroaniline (30.3g，0.1875mole) **替代**aniline**進行之，得到黃色針狀結晶為化合物 22** (31.0g，52.3%)，mp：152-153**℃。光譜數據如下：**MS *m/z*: M^+ 314.9, $(M+2)^+$ 317.0; IR (KBr) cm^{-1}: 3264.6 (NH), 1775.1 (C_3=O), 1643.9 (-C=$OOCH_2CH_3$); UV λ_{max} nm (MeOH) (log ε): 278.8 (4.40); $C_{13}H_{11}Cl_2NO_4$, calcd.(found) (%), C: 49.39 (48.57), H: 3.50 (3.29); ^{1}H-NMR ($CDCl_3$)δ: 1.37 (3H,t,J=7.2 Hz, -$COOCH_2C\underline{H}_3$), 4.35 (2H, q, J=7.2 Hz, -$COOC\underline{H}_2CH_3$), 4.64 (2H, s, H-5), 7.01-7.31 (3H, m, Ar-H).

Ethyl 2-(2',4'-dichloroanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (23) 之合成

比照化合物1之製造方法過程，而以2,4-dichloroanline (30.3g，0.1875mole)**替代**aniline**進行之，得到黃色針狀結晶為化合物 23** (30.4g，51.4%)，mp：178-179 **℃。光譜數據如下：**MS *m/z*: M^+ 314.9, $(M+2)^+$ 317.0; IR (KBr) cm^{-1}: 3271.5 (NH), 1751.5 (C_3=O), 1697.5 (-C=OOCH_2CH_3); UV λ_{max} nm (MeOH) (log ε): 284 (4.61); $C_{13}H_{11}Cl_2NO_4$, calcd.(found) (%), C: 49.39 (48.78), H: 3.50 (3.38); ^{1}H-NMR ($CDCl_3$) δ: 1.37(3H,t,J=7.2 Hz, -COO$CH_2C\underline{H}_3$), 4.37 (2H, q, J=7.2 Hz, -COO$C\underline{H}_2CH_3$), 4.70 (2H, s, H-2), 7.26 (1H, dd, J=8.8, 2.4 Hz, H-5′), 7.46 (1H, d, J=2.4 Hz, H-3′), 7.74 (1H,d,J=8.8 Hz, H-6′), 10.75 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 14.24 (-$COOCH_2\underline{C}H_3$), 60.58 (-$COO\underline{C}H_2CH_3$), 75.42 (C-5), 88.45 (C-3), 122.63 (C-6′), 125.67 (C-1′), 127.73 (C-3′), 129.50 (C-5′), 130.97 (C-4′), 131.09 (C-2′), 165.04 (C-2), 177.57 (C- $COOC_2H_5$), 188.06 (C-4).

(二) Ethyl 2-(substituted aniline)-4-oxo-5-methyl-4,5-dihydrofuran-3-carboxylate (24-26)

Ethyl 2-anilino-4-oxo-5-methyl-4,5-dihydrofuran-3-carboxylate (24) 之合成

取NaH (9.6g，0.4mole) (**預先以乾燥之** n-Hexane **洗去** NaH suspension **所含之** paraffin oil) **懸著於無水之** THF 60ml **中後，緩慢滴入** diethyl malonate (61ml，0.4mole) **與** THF 60ml **之混合溶液，當滴加完後冷卻至**10-12**℃，再慢慢滴加** 2-Chloropropionyl chloride (25.6ml，0.2mole) **之** THF 200ml **溶液，滴加完後保持低溫** (10-12**℃**) **一小時 隨後改用溫浴** (40-50**℃**) **溫之約一小時，再冷卻至** 10-12 **℃。將**aniline (17.4ml，0.1875mole) **之** THF 80ml **溶液滴入上述反應液中，於室溫攪拌一小時後，在水浴上加熱一小時，減壓濃縮去除大部份之** THF **後，倒入冰水，再以** $CHCl_3$ **萃取多次，其萃取液經水洗後，以無水** $MgSO_4$ **乾燥，濃縮後置於室溫下令其結晶，收集結晶用乙醇再結晶，收集淡黃色針狀結晶為化合物 24** (26.1g，53.5%)，mp：103-105**℃。光譜數據如下：**MS *m/z*: 261.0; IR (KBr) cm^{-1}: 2932.7 (NH), 1709.0 (C_3=O), 1658.9 (-C=OOCH_2CH_3); UV λ_{max} nm (MeOH) (log ε): 272(4.75); $C_{14}H_{15}NO_4$, calcd.(found) (%), C: 64.35 (63.32), H: 5.78 (5.43); ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7.2 Hz,$COOCH_2C\underline{H}_3$),1.55 (3H, d, J=7.0 Hz,C_5-CH_3), 4.34(2H, q, J=7.0 Hz, -$COO\underline{C}H_2CH_3$), 4.76 (2H, q, J=7.0 Hz, C_5-H), 7.19-7.26 (1H, m, H-4′), 7.34-7.39 (4H, m, Ar-H), 10.27 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 14.22 (-$COOCH_2\underline{C}H_3$), 16.66 (C_5-$\underline{C}H_3$), 60.31 (-$COO\underline{C}H_2CH_3$), 83.87 (C-5), 86.15 (C-3), 121.08 (C-2′, C-6′), 125.77 (C-4′), 129.22 (C-3′, C-5′), 134.78 (C-1′), 165.71 (C-2), 175.97 (C-$\underline{C}OOC_2H_5$), 190.92 (C-4).

Ethyl 2-(3'-methoxyanilino)-4-oxo-5-methyl-4,5-dihydrofuran-3-carboxylate (25) 之合成

比照化合物24之製造方法過程，而以 *m*-anisidine (20ml，0.1875mole)**替代** aniline**進行之，得到黃色針狀結晶為化合物 25** (30.8g，56.5%)，mp：100-102 **℃。光譜數據如下：**MS *m/z*: 291.0; IR (KBr) cm^{-1}: 2932.7 (NH), 1759.6 (C_3=O), 1674.7 (-C=OOCH_2CH_3); UV λ_{max} nm (MeOH) (log ε): 271(4.83); $C_{15}H_{17}NO_5$, calcd.(found) (%), C: 61.84 (60.72), H: 5.88 (5.62); ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7.0 Hz, -$COOCH_2C\underline{H}_3$), 1.57 (3H, d, J=7.0 Hz, C_5-CH_3), 3.82 (3H, s, -OCH_3), 4.36 (2H, q, J=7.0 Hz, -$COO\underline{C}H_2CH_3$), 4.78 (1H, q, J=7.0 Hz, C_5-H), 6.77 (1H, dd, J=7.0, 2.4 Hz, H-6′), 6.94-6.99 (2H, m, H-2′, H-4′), 7.28 (1H, m, H-5′), 10.28 (1H, s, NH); ^{13}C-NMR ($CDCl_3$)δ:14.43(-$COOCH_2\underline{C}H_3$),16.88(C_5-$\underline{C}H_3$),55.41(-OCH_3), 60.56 (-$COO\underline{C}H_2CH_3$), 84.16 (C-5), 86.44 (C-3), 107.46 (C-2′), 111.22 (C-4′), 113.52 (C-6′), 130.24 (C-5′), 136.08 (C-1′), 160.33 (C-3′), 165.97 (C-2), 176.21 (C-$\underline{C}OOC_2H_5$), 191.14 (C-4).

Ethyl 2-(4'-methoxyanilino)-4-oxo-5-methyl-4,5-dihydrofuran-3-carboxylate (26) 之合成

比照化合物24之製造方法過程，而以 *p*-anisidine (20ml，0.1875mole)**替代** aniline**進行之，得到黃色針狀結晶為化合物 26** (29.7g，54.5%)，mp：109-111 **℃。光譜數據如下：**MS *m/z*: 291.0; IR (KBr) cm^{-1}: 3256.8 (NH), 1782.8 (C_3=O),

1667.0 (-C=OOCH$_2$CH$_3$); UV λ_{max} nm (MeOH) (log ε): 276 (4.47); $C_{15}H_{17}NO_5$, calcd.(found) (%), C: 61.84 (60.72), H: 5.88 (5.62); ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t,J=7.2 Hz, -COOCH$_2$C<u>H</u>$_3$), 1.53 (3H, d, J=7.0 Hz, C_5-CH$_3$), 3.79 (3H, s, -OCH$_3$), 4.33 (2H, q, J=7.2 Hz, -COOC<u>H</u>$_2$CH$_3$), 4.72 (1H, q, J=7.0 Hz, C_5-H), 6.90 (2H, dd, J=6.6, 2.4 Hz, H-2′, H-6′), 7.27 (2H, dd, J=6.6, 2.4 Hz, H-3′, H-5′), 10.28 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 14.24 (-COOCH$_2$<u>C</u>H$_3$), 16.68 (C_5-<u>C</u>H$_3$), 55.26 (-OCH$_3$), 60.22 (-COO<u>C</u>H$_2$CH$_3$), 83.71 (C-5), 85.80 (C-3), 114.32 (C-2′, C-6′), 123.05 (C-3′, C-5′), 127.53 (C-1′), 157.53 (C-4′), 165.72 (C-2), 175.70 (C-COOC$_2$H$_5$), 190.87 (C-4).