A Simple Synthesis of Dimethyl 2-Pyridone-4,5-dicarboxylate Derivatives

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1-Hydroxyphenyl-2-pyridone derivatives **8**, **10** and **11** were easily prepared by treatment of methyl isocrotonate derivatives **6** with base at room temperature in good yields.

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As a part of our studies on the synthesis of heterocyclic compounds [1], we recently reported the thermal cyclization of methyl isocrotonate derivatives [2]. We have now examined the behavior of these methyl isocrotonate derivatives to base and found that *N*-substituted phenyl-2-pyridones [3] were easily synthesized in fairly good yields. We describe the full details of our experimental results of these studies [4].

The cyclization product, a pyrido[1,2-*a*]quinoxaline derivative **2** [2] was prepared by stirring a solution of isocrotonate derivative **1** obtained by the reaction of *o*-phenylenediamine with dimethyl acetylenedicarboxylate (DMAD) and triethylamine in dichloromethane at room temperature in low yield as shown in Scheme 1.

Similarly, pyrido[1,2-*a*]pyrazine derivative **4a** [2] and pyrido[2,1-*c*]-1,4-oxazine derivative **4b** [2] were synthesized on treatment with triethylamine of **3a** or **3b** obtained by the reaction of 1,2-ethylenediamine or 2-aminoethanol with DMAD, respectively.

But isocrotonate derivatives **6** prepared by the reaction of *o*-aminophenols **5** with DMAD showed a different reactivity compared with **1** or **3** on treatment with base. Isocrotonate **6a** (R = Cl) was treated with triethylamine in dichloromethane and methanol at room temperature followed by silica gel column chromatography to give two products. It was confirmed that the minor product **7a** (3% yield) is a pyrido[2,1-*c*]-1,4-benzoxazine derivative by direct comparison with an authentic sample [2]. The major product **8a** (68% yield) has the empirical formula $C_{17}H_{14}ClNO_8$ which was derived from the elemental analysis and the mass spectral analysis. The ^{1}H-nmr spectrum of **8a** showed the presence of three methyl esters at δ 3.57, 3.80 and 3.92 (each s), three aromatic protons at δ 6.64-7.17 (m), a vinyl proton at δ 6.92 (s) and a hydroxy proton at δ 8.11

Scheme 1

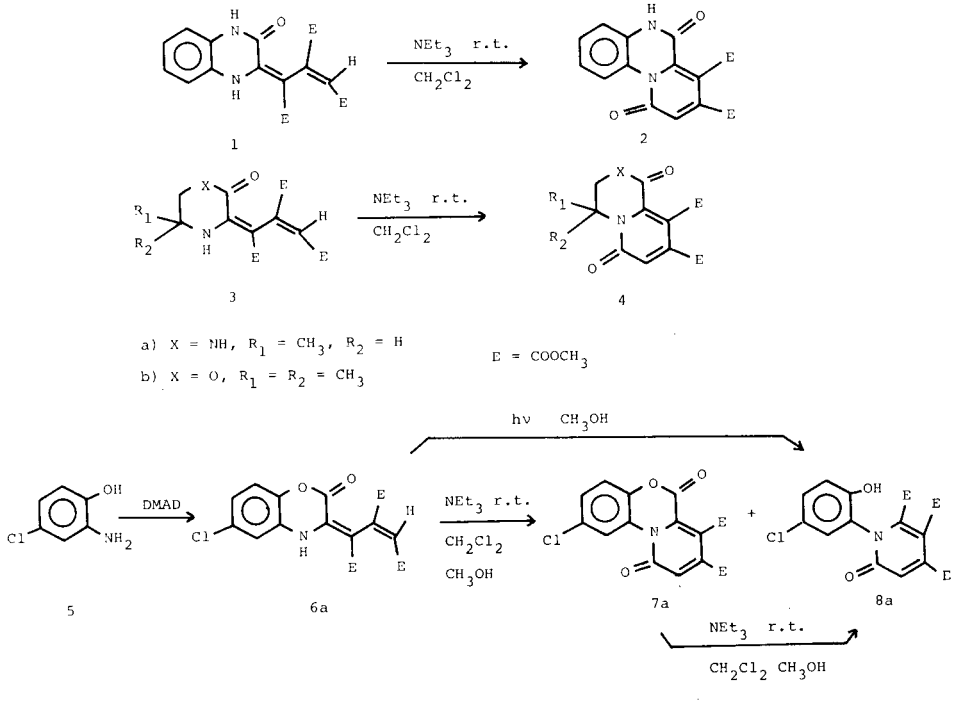

Table 1

2-Pyridone Derivatives **8**, **10** and **11**

Compound No.	R_1	R_2	Reaction [a] time (hour)	Yield [a] (%)	Mp (°C) [b]
8a	Cl	H	3 (16)	69 (49)	185-187
8b	H	H	3 (3)	63 (57)	132-133
8c	CH_3	H	3 (16)	80 (77)	143-145
8d	H	CH_3	3 (20)	58 (48)	154-156
10a	Cl	H	3	82	149-150
10b	H	H	4	87	157-158
10c	CH_3	H	5	90	172-174
10d	H	CH_3	5	45	174-175
11a	Cl	H	3	70	196-198
11b	H	H	1	55	198-199
11c	CH_3	H	1	87	177-179
11d	H	CH_3	3	52	222-223

[a] The values in parenthesis indicate the values obtained when methanol was not added to the reaction mixture. [b] Uncorrected.

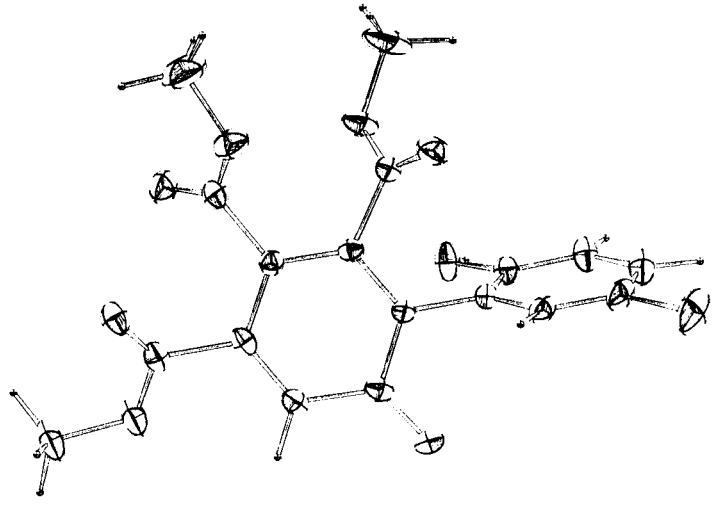

Figure. A Perspective Drawing of the Molecule of **8a**.

(br). The other spectral data are shown on Table 2 and in the experimental section. It was observed that **7a** was converted to **8a** by a similar treatment with triethylamine in dichloromethane and methanol in 90% yield. Furthermore, we could obtain **8a** by photolysis of **6a** in methanol at room temperature in 79% yield. It seemed most likely that the lactone ring of pyrido[2,1-*c*]-1,4-benzoxazine **7a** was cleaved by nucleophilic attack of methanol to give *N*-substituted phenyl-2-pyridone. The structure of **8a** was assigned to be trimethyl 1-(2-hydroxy-5-chloro)phenyl-2-pyridone-4,5,6-tricarboxylate and in order to confirm the structure, we carried out an X-ray crystallographic analysis.

Similarly, by treatment with triethylamine of **6b**, the pyrido[2,1-*c*]-1,4-benzoxazine **7b** (19% yield) and 2-pyridone derivative **8b** (63% yield) were obtained. When **6c** was treated in a similar manner, **7c** and **8c** were obtained in 14% and 79% yields, respectively. Further, **6d** gave **7d** and **8d** in 13% and 58% yields, respectively. Thus, trimethyl 1-hydroxyphenyl-2-pyridone-4,5,6-tricarboxylate derivatives **8a-d** were easily synthesized by the treatment

Scheme 2

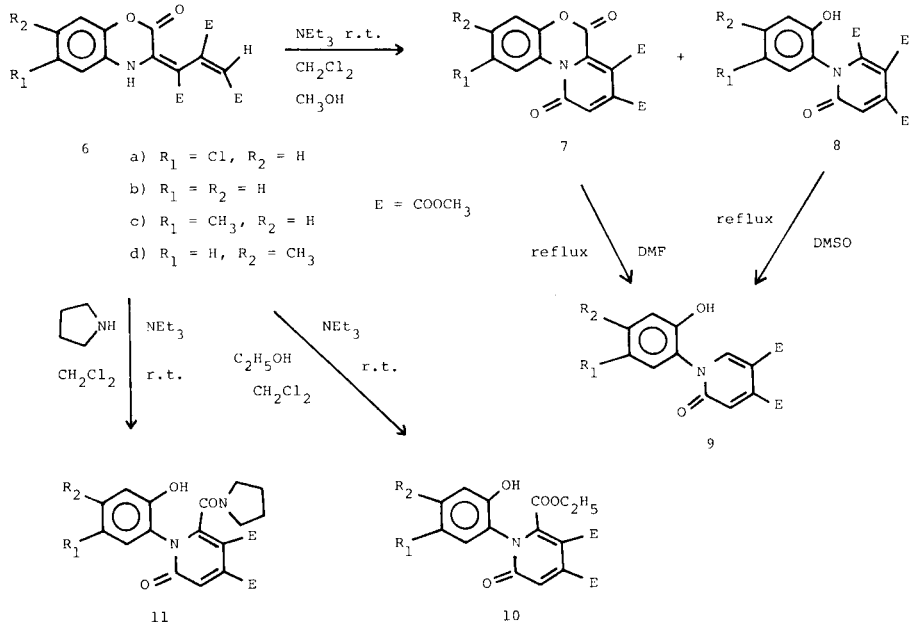

Table 2

Spectral Data for Compounds **8**, **9**, **10** and **11**

Compound No.	Molecular Formula MS (m/z, M^+)	IR (cm^{-1}) (Potassium bromide)	^{1}H-NMR (δ ppm) (Deuteriochloroform)
8a	$C_{17}H_{14}ClNO_6$ 395,397	3100, 1740, 1600	3.54, 3.80 and 3.92 (each 3H, s), 6.64-7.17 (3H, m), 6.92 (1H, s), 8.11 (1H, br)
8b	$C_{17}H_{15}NO_6$ 361	3250, 1730, 1665	3.40, 3.80 and 3.96 (each 3H, s), 6.60-7.20 (4H, m), 6.86 (1H, s), 7.54 (1H, br)
8c	$C_{18}H_{17}NO_6$ 375	3200, 1730, 1660	2.26, 3.52, 3.81 and 3.93 (each 3H, s), 6.82-7.23 (3H, m), 6.88 (1H, s), 7.54 (1H, br)
8d	$C_{18}H_{17}NO_6$ 375	3200, 1725, 1665	2.18, 3.52, 3.79 and 3.91 (each 3H, s), 6.52-6.88 (3H, s), 6.85 (1H, s), 7.46 (1H, br)
9	$C_{15}H_{13}NO_5$ 303	3400, 1720, 1660	[a] 3.74 and 3.83 (each 3H, s), 6.63 (1H, s), 6.92-7.32 (4H, m), 8.16 (1H, s), 8.36 (1H, br)
10a	$C_{18}H_{16}ClNO_6$ 409,411	3170, 1740, 1660	1.10 (3H, t, J = 7 Hz), 3.79 and 3.92 (each 3H, s), 4.04 (2H, q, J = 7 Hz), 6.65-7.22 (3H, m), 6.86 (1H, s), 8.34 (1H, br)
10b	$C_{18}H_{17}NO_6$ 375	3300, 1730, 1660	0.96 (3H, t, J = 7 Hz), 3.79 and 3.91 (each 3H, s), 3.92 (2H, q, J = 7 Hz), 6.70-7.28 (4H, m), 6.86 (1H, s), 7.80 (1H, br)
10c	$C_{19}H_{19}NO_6$ 389	3100, 1740, 1665	0.98 (3H, t, J = 7 Hz), 2.25, 3.80 and 3.92 (each 3H, s), 4.02 (2H, q, J = 7 Hz), 6.68-7.20 (3H, m), 6.88 (1H, s)
10d	$C_{19}H_{19}NO_6$ 389	3200, 1730, 1665	0.99 (3H, t, J = 7 Hz), 2.17, 3.79 and 3.91 (each 3H, s), 3.99 (2H, q, J = 7 Hz), 6.52-6.97 (3H, m), 6.85 (1H, s), 7.57 (1H, br)
11a	$C_{20}H_{19}ClN_2O_7$ 434,436	3100, 1725, 1690, 1630	1.70 (4H, m), 3.37 (4H, m), 3.79 and 3.94 (each 3H, s), 6.61-7.23 (3H, m), 6.85 (1H, s), 8.61 (1H, br)
11b	$C_{20}H_{20}N_2O_7$ 400	3150, 1720, 1685, 1630	1.75 (4H, m), 3.40 (4H, m), 3.76 and 3.93 (each 3H, s), 6.60-7.28 (4H,m), 6.85 (1H, s), 8.36 (1H, br)
11c	$C_{21}H_{22}N_2O_7$ 414	3200, 1725, 1690, 1630	1.70 (4H, m), 2.23 (3H, s), 3.44 (4H, m), 3.78 and 3.92 (each 3H, s), 6.67-7.08 (3H, m), 6.86 (1H, s), 7.99 (1H, br)
11d	$C_{21}H_{22}N_2O_7$ 414	3150, 1720, 1680, 1640	1.82 (4H, m), 2.26 (3H, s), 3.35 (4H, m), 3.79 and 3.92 (each 3H, s), 6.83-6.90 (3H, m), 6.85 (1H, s), 7.75 (1H, br)

[a] Deuteriodimethyl sulfoxide.

with triethylamine of methyl isocrotonate derivatives **6a-d** in fairly good yields. A most plausible mechanism for this reaction (**6** → **8**) involves the initial formation of the pyrido[2,1-*c*]-1,4-benzoxazine **7** followed by opening of the lactone ring by nucleophiles.

A solution of pyrido[2,1-*c*]-1,4-benzoxazine **7b** in di-

methylformamide was heated under reflux to give an almost single product on thin-layer chromatography. The ^{1}H-nmr spectrum of this new compound **9** (79% yield) showed the presence of two methyl esters at δ 3.72 (s) and 3.82 (s), two isolated vinyl protons at δ 6.63 (s) and 8.15 (s), four aromatic protons at δ 6.80-7.50 (m) and a hydroxy proton at δ 10.19 (s). These data suggested that this compound **9** is a ring-cleaved compound of the starting material **7b**. Thus, the structure of **9** was assigned as dimethyl 1-(*o*-hydroxyphenyl)-2-pyridone-4,5-dicarboxylate. This compound could be also prepared by the pyrolysis of **8b** in dimethyl sulfoxide in low yield.

When ethanol was added to the reaction mixture, **6** afforded the ethyl esters, 6-ethoxycarbonyl-2-pyridone derivatives **10**. Moreover, when pyrrolidine was used as base, **6** converted to the corresponding amides, 6-pyrrolidinocarbonyl-2-pyridone derivatives **11**.

In conclusion, 6-alkoxycarbonyl-(and 6-carbamoyl)-1-phenyl-2-pyridone derivatives were easily prepared by the treatment with base of the methyl isocrotonate derivatives which were obtained by the reaction of *o*-aminophenols with DMAD in good yields.

EXPERIMENTAL

Melting points were determined on a micro hot-stage apparatus (Mitamura) and are uncorrected. The ir spectra were recorded on a Hitachi 215 infrared spectrophotometer. The ^{1}H-nmr and ^{13}C-nmr spectra were measured on a JNM-FX 100 spectrometer (JEOL) with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ value. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. The low- and high-resolution mass spectra were obtained with a GCMS-9000 spectrometer (Shimadzu) and JMS-DX 300 instrument (JEOL).

The elemental analyses were done by the staff of the Analytical Center of the School of Pharmaceutical Sciences, Kitasato University, to whom our thank are due. The thin-layer chromatography (tlc) was performed with Merck precoated silica gel 60 F_{254} plates. The preparative tlc was done with the same commercial product, 20 x 20 cm, with a thickness of 0.25, 0.5 or 2.0 mm. For column chromatography, silica gel (Wakogel C-200, Waco Pure Chemical Industries) was used.

The photolysis was carried out in a flask with a 300 W high-pressure mercury lamp covered with a pyrex filter under nitrogen atmosphere.

General Procedure for the Treatment of **6** with Base.

To a solution of the appropriate isocrotonate **6** (1 mmole) in dry dichloromethane (15-25 ml) or dry alcohol-dichloromethane (1:1, 15-25 ml), triethylamine (0.5-1.2 mmoles) or pyrrolidine (3.0-5.0 mmoles) in dry dichloromethane (5.0-10.0 ml) was added. The reaction mixture was stirred at room temperature for 1-20 hours until disappearance of a spot of the starting material on tlc. After removal of the solvent and base by co-evaporation with benzene *in vacuo*, the residual product (crystalline solid or oil) was purified by column chromatography and/or preparative tlc, and finally recrystallization from an appropriate solvent.

The cyclic compounds **2** (22% yield), **4a** (50% yield) and **4b** (84% yield) were prepared according to the general procedure from **1**, **3a** or **3b**, respectively and the structures of these compounds were confirmed by direct comparison with the authentic samples [2].

Trimethyl 1-(2-Hydroxy-5-chloro)phenyl-2-pyridone-4,5,6-tricarboxylate **8a** (R_1 = Cl, R_2 = H).

Compound **6a** (2.56 g) was treated with triethylamine (0.5 ml) for 3 hours in a mixture of dichloromethane (50 ml) and methanol (50 ml). According to the general procedure, the residue was purified by column chromatography on silica gel (80 g) to give **7a** (73.6 mg, eluted with 5% ether in benzene) and **8a** (1.758 g, eluted with 10% ether in benzene) which was recrystallized from ethanol to afford pure analytical sample, mp 185-187° (white prisms); ^{13}C-nmr (deuteriochloroform): 53.12 (q), 53.36 (q x 2), 108.33 (s), 118.36 (d), 121.24 (d), 124.02 (s), 124.17 (s), 128.20 (d), 131.52 (d), 143.90 (s), 145.65 (s), 151.65 (s), 160.90 (s), 161.05, 163.29 (s), 165.43 (s).

Anal. Calcd. for $C_{17}H_{14}ClNO_8$: C, 51.60; H, 3.57; N, 3.54. Found: C, 51.61; H, 3.56; N, 3.41.

According to the general procedure, **6a** (3.0 g) was treated with triethylamine (0.5 ml) for 16 hours in dichloromethane (100 ml) to give **8a** (1.475 g).

Trimethyl 1-(2-Hydroxy)phenyl-2-pyridone-4,5,6-tricarboxylate **8b** (R_1 = R_2 = H).

Compound **6b** (0.1 g) was treated with triethylamine (0.05 ml) in a mixture of dichloromethane (10 ml) and methanol (10 ml) for 3 hours. According to the general procedure, the residue was purified by preparative tlc (ethyl acetate:benzene = 2:3) to give **7b** (17.3 mg) and **8b** (63.2 mg), mp 132-133° (white rods from dichloromethane-ether); ^{13}C-nmr (deuteriochloroform): 53.02 (q), 53.21 (q x 2), 107.69 (s), 117.44 (d), 119.88 (d), 121.14 (d), 123.53 (s), 128.40 (d), 131.57 (d), 143.60 (s), 146.19 (s), 152.67 (s), 161.10 (s x 2), 163.49 (s), 165.68 (s).

Anal. Calcd. for $C_{17}H_{15}NO_8$: C, 56.51; H, 4.18; N, 3.88. Found: C, 56.35; H, 4.14; N, 3.74.

According to the general procedure, **6b** (1.0 g) was treated with triethylamine (0.25 ml) in dichloromethane (40 ml) for 3 hours to give **8b** (0.57 g).

Trimethyl 1-(2-Hydroxy-5-methyl)phenyl-2-pyridone-4,5,6-tricarboxylate **8c** (R_1 = CH_3, R_2 = H).

Compound **6c** (3.0 g) was treated with triethylamine (0.5 ml) in a mixture of dichloromethane (150 ml) and methanol (150 ml) for 3 hours. According to the general procedure, the residue was purified by column chromatography on silica gel (90 g) to give **7c** (0.398 g, eluted with 10% ether in benzene) and **8c** (2.386 g, eluted with 15% ether in benzene), mp 143-145° (pale yellow prisms from dichloromethane-ether); ^{13}C-nmr (deuteriochloroform): 20.22 (q), 52.97 (q), 53.12 (q), 53.21 (q), 107.74 (s), 117.44 (d), 121.14 (d), 123.43 (s), 128.40 (d), 129.67 (s), 132.06 (d), 143.36 (s), 146.00 (s), 150.09 (s), 161.05 (s), 161.20 (s), 163.49 (s), 165.63 (s).

Anal. Calcd. for $C_{18}H_{17}NO_8$: C, 57.60; H, 4.57; N, 3.73. Found: C, 57.77; H, 4.56; N, 3.71.

According to the general procedure, **6c** (1.0 g) was treated with triethylamine (0.25 ml) in dichloromethane (40 ml) for 16 hours to

give **8c** (0.77 g).

Trimethyl 1-(2-Hydroxy-4-methyl)phenyl-2-pyridone-4,5,6-tricarboxylate **8d** (R_1 = H, R_2 = CH_3).

Compound **6d** (0.1 g) was treated with triethylamine (0.05 ml) in a mixture of dichloromethane (10 ml) and methanol (10 ml) for 3 hours. According to the general procedure, the residue was purified by preparative tlc (ethyl acetate:benzene = 1:3) to give **7d** (12 mg) and **8d** (58 mg), mp 154-156° (white prisms from dichloromethane-ether); ^{13}C-nmr (deuteriochloroform): 21.30 (q), 52.97 (q), 53.21 (q x 2), 107.64 (s), 118.07 (d), 120.75 (d), 121.05 (d and s), 127.87 (d), 141.90 (s), 143.66 (s), 146.43 (s), 152.23 (s), 161.34 (s x 2), 163.44 (s), 165.73 (s).

Anal. Calcd. for $C_{18}H_{17}NO_8$: C, 57.60; H, 4.57; N, 3.73. Found: C, 57.65; H, 4.84; N, 3.65.

According to the general procedure, **6d** (0.9 g) was treated with triethylamine (0.25 ml) in dichloromethane (40 ml) for 20 hours to give **8d** (0.432 g).

Treatment of **7a** with Triethylamine.

A solution of **7a** (0.1 g) and triethylamine (0.05 ml) in a mixture of dichloromethane (20 ml) and methanol (20 ml) was stirred at room temperature overnight. After removal of the solvent *in vacuo*, the residue was purified by preparative tlc (ethyl acetate:benzene = 1:3) to give **8a** (98 mg) which was identified by comparison with the authentic sample.

Photolysis of **6a**.

A solution of **6a** (0.5 g) in dry methanol (500 ml) was irradiated for 6 hours at room temperature under a nitrogen atmosphere. After removal of the solvent *in vacuo*, the residual oil purified by preparative tlc (ethyl acetate:benzene = 1:3) to give **8a** (0.398 g).

Dimethyl 1-(2-Hydroxy)phenyl-2-pyridone-4,5-dicarboxylate **9**.

A solution of **7b** (32.9 mg) in dimethylformamide (10 ml) was stirred under refluxing for 7 hours. After removal of the solvent *in vacuo*, extraction of the reaction product with dichloromethane and methanol followed by evaporation of the solvent *in vacuo* to afford a crystalline solid (24 mg, 79%) which was recrystallized from methanol to give pure sample **9**, mp 223-224° (white needles); ^{13}C-nmr (deuteriodimethyl sulfoxide): 52.63 (q), 53.21 (q), 106.23 (s), 116.90 (d), 118.61 (d), 119.68 (d), 127.04 (s), 128.65 (d), 130.89 (d), 144.19 (s), 146.29 (d), 152.13 (s), 160.71 (s), 163.59 (s), 166.51 (s).

Anal. Calcd. for $C_{15}H_{13}NO_6$: C, 59.40; H, 4.32; N, 4.62. Found: C, 59.22; H, 4.22; N, 4.64.

This compound **9** was also prepared by the thermal reaction of **8b**.

A solution of **8b** (150 mg) in dimethyl sulfoxide (10 ml) was heated under reflux for 4 hours and after removal of the solvent *in vacuo*, the residue was subjected to preparative tlc (ethyl acetate:benzene = 1:3) to give unknown product (13 mg), **9** (18 mg) and **8b** (34 mg).

Dimethyl 1-(2-Hydroxy-5-chloro)phenyl-6-ethoxycarbonyl-2-pyridone-4,5-dicarboxylate **10a** (R_1 = Cl, R_2 = H).

Compound **6a** (0.2 g) was treated with triethylamine (0.1 ml) in a mixture of dichloromethane (10 ml) and ethanol (10 ml) for 3 hours. According to the general procedure, the residue was purified by preparative tlc (ethyl acetate:benzene = 1:3) to give **10a** (0.169 g), mp 149-150° (colorless cubes from dichloromethane-ether); ^{13}C-nmr (deuteriochloroform): 13.40 (q), 53.02 (q), 53.31 (q), 63.15 (t), 108.03 (s), 118.27 (d), 121.05 (d), 123.92 (s), 128.50 (d), 131.47 (d), 143.90 (s), 145.85 (s), 151.79 (s), 160.42 (s), 161.05 (s), 163.34 (s), 165.49 (s).

Anal. Calcd. for $C_{18}H_{16}ClNO_8$: C, 52.74; H, 3.94; N, 3.42. Found: C, 52.85; H, 3.85; N, 3.23.

Dimethyl 1-(2-Hydroxy)phenyl-6-ethoxycarbonyl-2-pyridone-4,5-dicarboxylate **10b** (R_1 = R_2 = H).

Compound **6b** (0.21 g) was treated with triethylamine (0.1 ml) in a mixture of dichloromethane (10 ml) and ethanol (10 ml) for 4 hours. According to the general procedure, the residue was purified by preparative tlc (ethyl acetate:benzene = 1:3) to give **10b** (0.19 g), mp 157-158° (white cubes from dichloromethane-ether); ^{13}C-nmr (deuteriochloroform): 13.40 (q), 52.92 (q), 53.26 (q), 62.96 (t), 107.69 (s), 117.44 (d), 119.83 (d), 121.09 (d), 123.63 (s), 128.70 (d), 131.57 (d), 143.66 (s), 146.39 (s), 152.87 (s), 160.71 (s), 161.20 (s), 163.59 (s), 165.78.

Anal. Calcd. for $C_{18}H_{17}NO_8$: C, 57.60; H, 4.57; N, 3.73. Found: C, 57.70; H, 4.53; N, 3.81.

Dimethyl 1-(2-Hydroxy-5-methyl)phenyl-6-ethoxycarbonyl-2-pyridone-4,5-dicarboxylate **10c** (R_1 = CH_3, R_2 = H).

Compound **6c** (1.0 g) was treated with triethylamine (0.25 ml) in a mixture of dichloromethane (20 ml) and ethanol (20 ml) for 5 hours. According to the general procedure, the residue was purified by column chromatography on silica gel (35 g) to give **10c** (0.935 g, eluted with 10% ether in benzene), mp 172-174° (white rods from ethanol); ^{13}C-nmr (deuteriochloroform): 13.68 (q), 20.55 (q), 53.25 (q), 53.60 (q), 63.17 (t), 107.85 (s), 117.54 (d), 121.35 (d), 123.53 (s), 129.05 (d), 129.63 (s), 132.39 (d), 143.84 (s), 146.66 (s), 150.77 (s), 161.04 (s), 161.45 (s), 163.92 (s), 166.09 (s).

Anal. Calcd. for $C_{19}H_{19}NO_8$: C, 58.61; H, 4.92; N, 3.60. Found: C, 58.71; H, 4.92; N, 3.60.

Dimethyl 1-(2-Hydroxy-4-methyl)phenyl-6-ethoxycarbonyl-2-pyridone-4,5-dicarboxylate **10d** (R_1 = H, R_2 = CH_3).

Compound **6d** (0.9 g) was treated with triethylamine (0.25 ml) in a mixture of dichloromethane (20 ml) and ethanol (20 ml) for 5 hours. According to the general procedure, the residue was purified by column chromatography on silica gel (30 g) to give **10d** (0.418 g, eluted with 10% ether in benzene), mp 174-175° (white needles from dichloromethane-ether); ^{13}C-nmr (deuteriochloroform): 13.35 (q), 21.30 (q), 52.87 (q), 53.21 (q), 62.86 (t), 107.64 (s), 118.07 (d), 120.66 (d), 121.00 (d), 121.14 (s), 128.06 (d), 141.90 (s), 143.66 (s), 146.53 (s), 152.37 (s), 160.71 (s), 161.40 (s), 163.54 (s), 165.68 (s).

Anal. Calcd. for $C_{19}H_{19}NO_8$: C, 58.61; H, 4.92; N, 3.60. Found: C, 58.85; H, 4.87; N, 3.66.

Dimethyl 1-(2-Hydroxy-5-chloro)phenyl-6-pyrrolidinocarbonyl-2-pyridone-4,5-dicarboxylate **11a** (R_1 = Cl, R_2 = H).

Compound **6a** (1.0 g) was treated with pyrrolidine (1.0 ml) in dichloromethane (40 ml) for 3 hours. According to the general procedure, the residue was purified by preparative tlc (ethyl acetate) to give **11a** (0.768 g), mp 196-198° (white needles from ethanol); ^{13}C-nmr (deuteriodimethyl sulfoxide): 23.49 (t), 25.00 (t), 44.98 (t), 46.83 (t), 52.82 (q), 53.07 (q), 104.43 (s), 117.20 (d), 119.39 (d), 121.53 (s), 124.26 (s), 130.11 (d), 130.50 (d), 143.27 (s), 149.55 (s), 152.23 (s), 158.47 (s), 159.45 (s), 163.49 (s), 165.68 (s).

Anal. Calcd. for $C_{20}H_{19}ClN_2O_7$: C, 55.24; H, 4.40; N, 6.44. Found: C, 55.54; H, 4.36; N, 6.46.

Dimethyl 1-(2-Hydroxy)phenyl-6-pyrrolidinocarbonyl-2-pyridone-4,5-dicarboxylate **11b** (R_1 = R_2 = H).

Compound **6b** (1.0 g) was treated with pyrrolidine (0.5 ml) in dichloromethane (40 ml) for 1 hour. According to the general procedure, the residue was purified by preparative tlc (ethyl acetate) to give **11b** (0.61 g), mp 198-199° (white rods from dichloromethane-ether); ^{13}C-nmr (deuteriochloroform): 23.98 (t), 25.39 (t), 45.27 (t), 47.12 (t), 52.87 (q), 53.16 (q), 107.25 (s), 117.20 (d), 120.07 (d), 123.68 (d), 129.37 (d), 131.03 (d), 143.75 (s), 149.51 (s), 152.09 (s), 159.20 (s), 161.49 (s), 163.78 (s), 165.68 (s).

Anal. Calcd. for $C_{20}H_{20}N_2O_7$: C, 59.99; H, 5.04; N, 7.00. Found: C, 59.97; H, 4.98; N, 6.81.

Dimethyl 1-(2-Hydroxy-5-methyl)phenyl-6-pyrrolidinocarbonyl-2-pyridone-4,5-dicarboxylate **11c** (R_1 = CH_3, R_2 = H).

Compound **6c** (1.0 g) was treated with pyrrolidine (1.1 ml) in dichloromethane (40 ml) for 1 hour. According to the general procedure, the residue was purified by preparative tlc (ethyl acetate) to give **11c** (0.964 g), mp 177-179° (white powder from ethanol); ^{13}C-nmr (deuteriochloroform): 20.58 (q), 24.42 (t), 25.83 (t), 45.79 (t), 47.61 (t), 53.37 (q), 53.66 (q), 108.03 (s), 117.42 (d), 120.53 (d), 123.82 (s), 130.04 (s and d) , 132.04 (d), 144.19 (s), 150.00 (s), 150.30 (s), 159.86 (s), 162.10 (s), 164.50 (s), 166.27 (s).

Anal. Calcd. for $C_{21}H_{22}N_2O_7$: C, 60.86; H, 5.35; N, 6.76. Found: C, 61.06; H, 5.35; N, 6.66.

Dimethyl 1-(2-Hydroxy-4-methyl)phenyl-6-pyrrolidinocarbonyl-2-pyridone-4,5-dicarboxylate **11d** (R_1 = H, R_2 = CH_3).

Compound **6d** (0.9 g) was treated with pyrrolidine (1.0 ml) in dichloromethane (40 ml) for 3 hours. According to the general procedure, the residue was purified by preparative tlc (ethyl acetate) to give **11d** (0.516 g), mp 222-223° (colorless plates from dichloromethane-ether); ^{13}C-nmr (deuteriochloroform): 21.34 (q), 23.98 (t), 25.44 (t), 45.61 (t), 47.76 (t), 52.78 (q), 53.07 (q), 105.55 (s), 119.58 (d), 120.51 (d), 120.95 (d), 121.73 (s), 126.16 (d), 141.85 (s), 143.17 (s), 148.82 (s), 152.57 (s), 160.12 (s), 161.10 (s), 163.88 (s), 165.97 (s). The high-resolution ms showed m/z 414.14218 (Calcd. for $C_{21}H_{22}N_2O_7$ is 414.14255).

Anal. Calcd. for $C_{21}H_{22}N_2O_7$: C, 60.86; H, 5.35; N, 6.76. Found: C, 60.65; H, 5.15; N, 6.40.

X-Ray Analysis.

A crystal of compound **8a** belongs to the monoclinic, space group $P2_1/a$, and Z = 4, a = 12.056(1)Å, b = 18.034(3)Å, c = 8.931(1)Å, β = 105.76(1)°. A specimen of **8a** with the approximate dimension 0.2 x 0.2 x 0.2 mm was used for the intensity measurements. Three dimensional intensity data for 2θ values within 150° were collected of a RIGAKU automatic four-cycle diffractometer with graphite monochromated Cu-Kα radiation by the 2θ-ω scan method at a 2 scan rate of 4°/minute. A total of 3429 independent reflections were collected. Reflections having an intensity exceeding the corresponding standard deviations by a factor of three were treated as observed. 2610 reflections were retained and corrected for Lorentz and polarization factors but not for absorption factors.

The structure of **8a** was determined by the symbolic addition method [5]. Five cycles of least-squares refinement with isotropic temperature factors resulted in an R value of 0.160. Anisotropic thermal parameters were introduced for all non-hydrogen atoms, and the R value was reduced to 0.097. Refinement with anisotropic temperature factors for non-hydrogen atoms and isotropic thermal factors for hydrogen atoms gave the final R values of 0.068.

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