Synthesis of *C*-nor-4,6-Secocamptothecin and Related Compounds

Takushi Kurihara*, Hirokatsu Tanno, Shigetaka Takemura,
Shinya Harusawa and Ryuji Yoneda

Osaka University of Pharmaceutical Sciences,
2-10-65, Kawai, Matsubara, Osaka 580, Japan

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C-nor-4,6-Secocamptothecin **2**, 4-ethyl-4-hydroxy-6-(2-quinolinyl)-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-dione, lacking the *C*-ring of camptothecin **1**, and its related compounds **3** and **4** were prepared from ethyl quinoline-2-carboxylate **7**. By an analogous reaction sequences, synthesis of 6-(2-pyridinyl)-1*H*-pyrano[3,4-*c*]-pyridine-3,8(4*H*,7*H*)-dione derivatives **5** and **6**, which contain the B, D, and E ring of **1**, were achieved.

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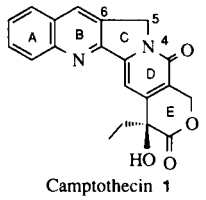
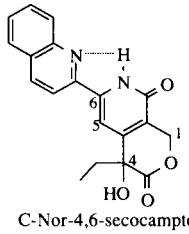
The antitumor alkaloid camptothecin (CPT) **1**, a known inhibition of mammalian topoisomerase I, was first isolated in 1966 from *Camptotheca acuminata (Nyssaceae)* [1]. The clinical utility of **1** as an anticancer agent has been investigated, but its toxicity ruled out for the cancer treatment [2]. Thus, modifications of the structure of **1** have been done to investigate new derivatives with potent antitumor activity [2,3]. It is well known that although α-hydroxylactone portion is necessary for antitumor activity, the A and B rings appear to be crucial since CDE-ring analogs of **1** have no useful activity [4]. It has been demonstrated that a compound having a 6-membered ring in the *C*-ring of camptothecin **1** is significantly inactivated because of the lack of the planarity of the whole molecule [5].

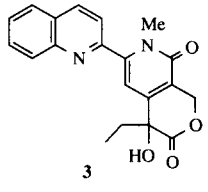
Formula 1



Camptothecin **1**



C-Nor-4,6-secocamptothecin **2**



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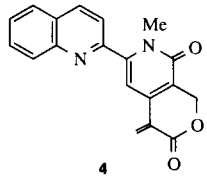

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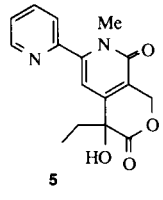

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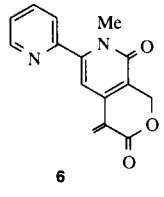

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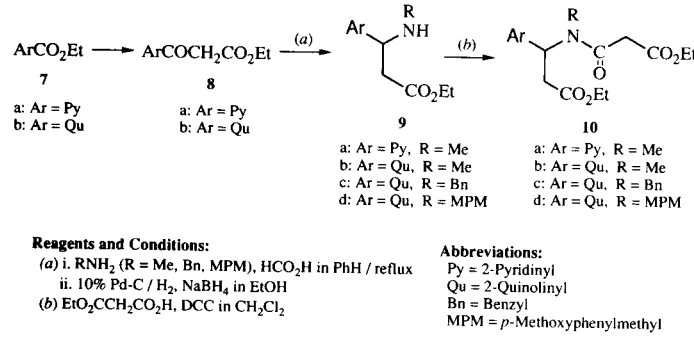
We designed, therefore, 6-(2-quinolinyl)pyridone **2**, which is a des-*C*-ring analog of camptothecin **1**, as a compound related to **1** with potent biological activity. Because the hydrogen bond formation between quinoline nitrogen atom and pyridone N-H group should make possible to retain a plane molecule. From these points of view, we now describe the synthesis of *C*-nor-4,6-secocamptothecin **2**, 5,6-secocamptothecin **3** and the corresponding pyridine derivative **5**, lacking the A and *C*-rings of **1**.

Synthesis of the BDE Ring Analogs of CPT **1**.

We first investigated the synthesis of the BDE ring analogs of **1**. The reaction of β-keto ester **8a**, obtained by Helbling's method [6], with methyl amine in the presence of formic acid in refluxing benzene gave enamine, which was subsequently hydrogenated under the initial pressure of 1 Kg/cm^2 with a combination of sodium borohydride and 10% palladium on carbon in ethanol afforded amine **9a** in good yield [7] (Scheme 1). Condensation of **9a**, without purification, with malonic acid monoethyl ester in the presence of dicychlohexylcarbodiimide (DCC) gave the amide **10a** in 84% yield from **8a**. Dieckmann condensation of **10a** with sodium ethoxide at room temperature

Scheme 1



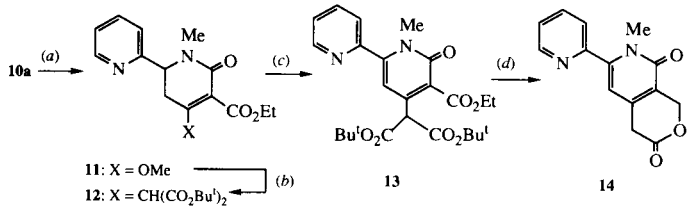
Reagents and Conditions:
(*a*) i. RNH_2 (R = Me, Bn, MPM), HCO_2H in PhH / reflux
ii. 10% Pd-C / H_2, $NaBH_4$ in EtOH
(*b*) $EtO_2CCH_2CO_2H$, DCC in CH_2Cl_2

Abbreviations:
Py = 2-Pyridinyl
Qu = 2-Quinolinyl
Bn = Benzyl
MPM = *p*-Methoxyphenylmethyl

appeared to proceed smoothly by monitoring on tlc, but the product could not be isolated in a pure form. Therefore, the reaction mixture was carefully treated with 10% hydrochloric acid for neutralization followed by ethereal

diazomethane solution to give methyl ether **11** (mp 151-155°) in 75% overall yield (Scheme 2). The ^{1}H nmr spectrum of **11** showed the methoxy protons at δ 3.00, C-5 protons at δ 3.11 (d, J = 3.5 Hz) and 3.13 (d, J = 6.7 Hz), and C-6 proton at δ 4.65 (dd, J = 3.5 and 6.7 Hz). Substitution of **11** with di-*tert*-butyl malonate in the presence of sodium hydride in refluxing dioxane afforded malonate **12** (85%), which was then treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene to give pyridone **13** in 78% yield. The lactone formation to lead product **14** was principally performed according to the method developed by Winterfeldt [8] in the total synthesis of CPT **1**. Namely, reduction of **13** with diisobutylaluminum hydride (DIBAL) in dimethoxyethane (DME) at −78° followed by treatment with sodium borohydride in methanol. The reaction was monitored by tlc and, when completed, trifluoroacetic acid (TFA) was added to the reaction mixture to give lactone **14** [mp 234-237°; ir: 1720 and 1660 (CO) cm^{-1}] with liberation of butene and carbon dioxide in 46% overall yield. The spectral properties and elemental analysis are consistent with structure **14**.

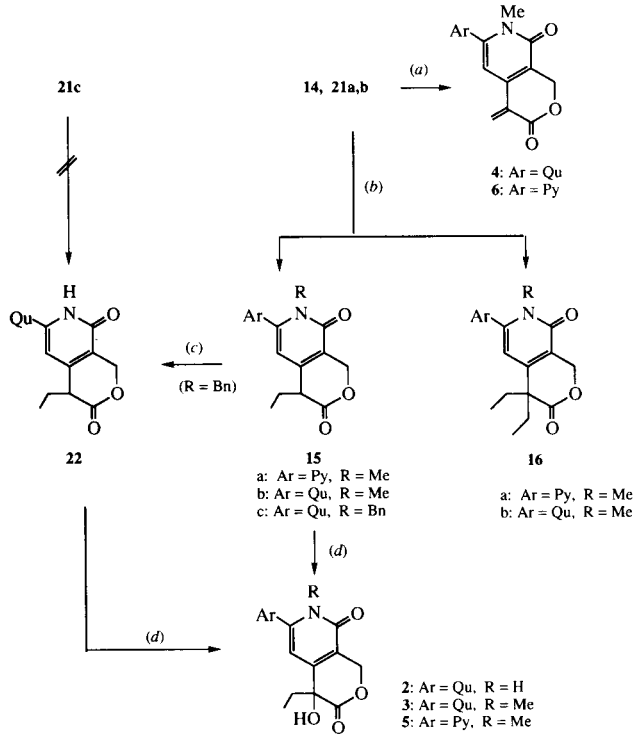
Scheme 2



Reagents and Conditions:
(*a*) i. NaOEt in EtOH; ii. H_3O^+; iii. CH_2N_2
(*b*) $CH_2(CO_2Bu^t)_2$, NaH in dioxane / reflux
(*c*) DDQ in PhH / reflux
(*d*) i. DIBAL in DME / -78°; ii. $NaBH_4$; iii. CF_3CO_2H

Previously, Sugasawa *et al* reported [9] that the one-pot ethylation-hydroxylation on the lactone ring have successfully been done in their total synthesis of the CPT **1**. Thus, the one-pot ethylation-hydroxylation of **14** was attempted [an oxygen stream in the presence of ethyl iodide and sodium hydride], but the target compound **5** was not obtained, unfortunately. Then, we turned our attention to obtain **5** *via* a stepwise route. Reaction of **14** with ethyl iodide in the presence of lithium hydride in dimethylformamide (DMF) [8] gave a mixture of monoethyl lactone **15a** [m/z 284 (M$^+$)] (47%) and diethyl lactone **16a** [m/z 312 (M$^+$)] (35%), together with recovery of the starting lactone **14** (17%). It was best to use lithium hydride as the base to minimize the production of diethyl lactone **16a**. Hydoxylation of **15a** with an oxygen stream in the presence of copper(II) chloride and 40% aqueous diethylamine solution [10] or 30% hydrogen peroxide in the presence of potassium *tert*-butoxide [11] gave a complex mixture, from which **5** could not be isolated. Finally, the desired compound **5**, mp 165-166°, was successfully obtained by treatment of **15a** with an oxygen stream in the presence of copper(II) acetate and triethylamine in methanol [12] at room temperature in 60% yield. The structure of **5** was determined by elemental analysis and spectroscopic data [ir: 3275 (OH), 1740 and 1640 (CO) cm^{-1}, and ^{1}H nmr: δ 0.96 (t, J = 7.5 Hz, CH_2CH_3), 1.80 (m, CH_2CH_3), and 3.65 (s, OH)]. As

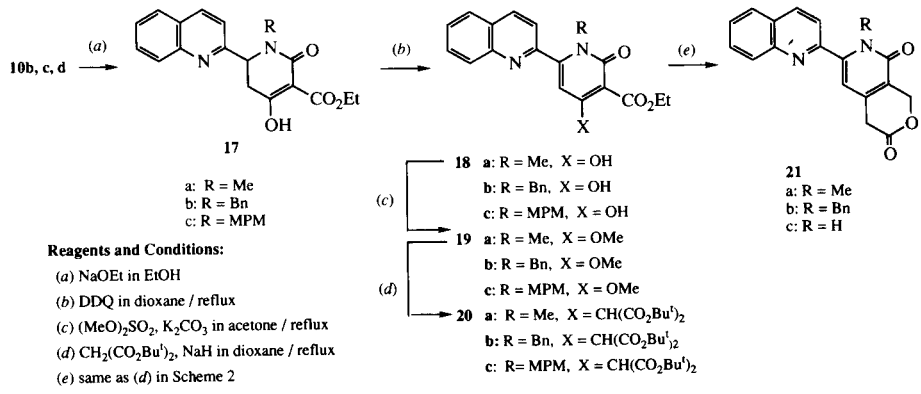
Scheme 3



Reagents and Conditions:
(*a*) PhNHMe CF_3CO_2H, $(HCHO)_n$ in THF / reflux
(*b*) EtI / LiH in DMF / 0°
(*c*) 47% HBr / reflux
(*d*) O_2, $Cu(OAc)_2$, Et_3N in MeOH

generally known, many natural products which contain the α-methylene-γ-butyrolactone ring exhibit interesting biological activity, because this moiety undergoes a Michael reaction with biological nucleophiles [13]. α-Methylene lactone **6** should be a strong Michael acceptor, because this methylene group also conjugates with the pyridone carbonyl group. Thus, for biological interest, α-methylene lactone **6** was synthesized. A number of methods for the preparation of α-methylenecarbonyl compounds have been described [14]. A simple, direct methylene transfer reaction using *N*-methylanilinium trifluoroacetate and paraformaldehyde is reported for the preparation of methylene ketones and aldehydes [15]. Although it is said that this method is not applicable to γ- or δ-lactones [15], δ-lactones **14** was successfully converted into α-methylene lac-

Scheme 4



tone **6** in 74% yield by this method. The ^{1}H nmr spectrum exhibited the signals due to two terminal methylene protons and C-5 proton at δ 6.23, 6.41, and 6.75 (each 1H, each s) (Scheme 3).

Synthesis of 5,6-Secocamptothecin and Related Compounds.

Syntheses of *C*-nor-4,6-secocamptothecin **2**, 5,6-secocamptothecin **3**, and the α-methylenelactone **4** were ac-

Table 1

Physical Constants, IR and Mass Spectral Data for 1*H*-Pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-diones

Compound	Molecular Formula (MW)	Mp, °C [a]	Calculated %/Found C	H	N	IR cm^{-1} CO	MS (M+)
2	$C_{19}H_{16}N_2O_4 \cdot 1/3\ H_2O$ (342.34)	244-246 [$CHCl_3$–MeOH–Et_2O]	66.67 66.41	4.71 4.64	8.18 8.09	1730, 1640	336
3	$C_{20}H_{18}N_2O_4$ (350.36)	181-182 [*n*-PrOH]	68.56 68.49	5.18 5.16	8.00 7.94	3460, 1720, 1645	350
4	$C_{19}H_{14}N_2O_3$ (318.32)	240-243 [MeCN]	71.69 71.48	4.43 4.50	8.80 8.91	1720, 1650	318
5	$C_{16}H_{16}N_2O_4$ (300.30)	165-166 [2-PrOH–Et_2O]	63.99 63.73	5.37 5.33	9.33 9.34	3275, 1740, 1640	300
6	$C_{15}H_{12}N_2O_3$ (268.26)	219-220 [MeCN]	67.15 67.38	4.51 4.63	10.44 10.40	1710, 1655	268
14	$C_{14}H_{12}N_2O_3$ (256.25)	234-237 [2-PrOH]	65.62 65.67	4.72 4.77	10.93 10.87	1720, 1660	256
15a	$C_{16}H_{16}N_2O_3 \cdot 1/10\ H_2O$ (286.10)	152-154 [2-PrOH]	67.16 67.16	5.70 5.69	9.85 9.79	1725, 1650	284
15b	$C_{20}H_{18}N_2O_3$ (334.36)	151-153 [EtOAC]	71.84 71.97	5.43 5.44	8.38 8.42	1720, 1640	334
15c	$C_{26}H_{22}N_2O_3$ (410.45)	oil [c]				1730 [b], 1650	410
16a	$C_{18}H_{20}N_2O_3$ (312.36)	232-235 [EtOH]	69.21 69.28	6.45 6.53	8.96 8.74	1730, 1650	312
16b	$C_{22}H_{22}N_2O_3$ (362.41)	230-232 [MeOH]	72.91 72.93	6.12 6.10	7.73 7.70	1720, 1650	362
21a	$C_{18}H_{14}N_2O_3$ (306.31)	237-238 [$CHCl_3$–MeOH]	70.58 70.75	4.61 4.59	9.15 9.14	1730, 1650	306
21b	$C_{24}H_{18}N_2O_3$ (382.40)	169-171 [EtOH]	75.38 75.34	4.74 4.75	7.33 7.34	1730, 1660	382
21c	$C_{17}H_{12}N_2O_3$ (292.28)	272-278 dec [$CHCl_3$–MeOH]	69.85 69.57	4.14 4.12	9.59 9.37	1740, 1610	292
22	$C_{19}H_{16}N_2O_3 \cdot 1/2\ H_2O$ (329.34)	210-213 [$CHCl_3$–Et_2O]	69.29 68.96	5.20 4.87	8.51 8.48	1710, 1640	320

[a] Crystallization solvent in parentheses. [b] In Neat. [c] High Resolution ms Calcd. for $C_{26}H_{22}N_2O_3$: 410.1630. Found: 410.1626.

complished from ethyl 2-quinolinecarboxylate **7b** *via* analogous sequences to those used for the preparation of pyridine derivatives. Amides **10b-d** were prepared from **7b** in a similar manner as described for the preparation of **10a** (Scheme 1). Treatments of **10b-d** with sodium ethoxide at room temperature gave the Dieckmann products **17a-c** in a pure form as an oil, respectively (Scheme 4). However, in contrast to the case of **10a**, methylation of **17a-c** with diazomethane in ether or with dimethyl sulfate-potassium carbonate in acetone did not give the desired products, only a complex mixture being obtained. Thus, dihydropyridones **17a-c** were first dehydrogenated with DDQ in refluxing benzene to give hydroxypyridiones **18a-c** (80-86% yields), which were readily methylated with dimethyl sulfate-potassium carbonate in acetone to give methyl ethers **19a-c** in 77-90% yields. Substitution of **19a-c** with di-*tert*-butyl malonate as described for the preparation of **13** gave **20a-c** in 62-77% yields. The resulting malonates **20a,b** were subjected to the sequences as described for the preparation of **14** to give lactones **21a(b)** [m/z 306 (382) (M^+)] in 62 (85%) overall yield, respectively. On the other hand, reaction of **20c** under the same reaction conditions gave lactone **21c** [m/z 292 (M^+)] with cleavage of the methoxyphenylmethyl (MPM) group in 73% overall yield.

The structural determination of lactones **21a-c** was performed by comparing the spectral data with those of **14**. As described for the ethylation of **14**, lactone **21a** was ethylated with ethyl iodide in the presence of lithium hydride gave a mixture of monoethyl lactone **15b** [m/z 334 (M^+)] (27%) and diethyl lactone **16b** [m/z 362 (M^+)] (5%), accompanied with the starting material **21a** (56%). However, it was very difficult to determine the optimum condition for monoethylation. Oxidation of **15b** with oxygen-copper(II) acetate-triethylamine gave the desired product **3** (mp 181-182°) in 57% yield, whose structure was determined as 4-ethyl-4-hydroxy-7-methyl-6-(2-quinolinyl)-1*H*-pyrano-[3,4-*c*]pyridine-3,8(4*H*,7*H*)-dione on the basis of the spectral data and elemental analysis. For biological interests, the α-methylenelactone **4** was synthesized by treatment of **21a** with *N*-methylanilinium trifluoroacetate and paraformaldehyde in 85% yield (Scheme 3).

Finally, we attempted the synthesis of *C*-nor-4,6-secocamptothecin **2**, which was expected to have a plane molecule by the formation of an intramolecular hydrogen bond as depicted in Formula 1. Direct ethylation of **21c** gave none of the desired 4-ethyl derivative **22** with only complex mixture being obtained, because the pyridone ring also has an active hydrogen. Therefore, *N*-benzyl lactone **21b** was selected as the starting material. Ethylation of **21b** with ethyl iodide in the presence of lithium hydride efficiently gave the monoethyl lactone **15c** in 45% yield with the recovery of **21b** in 46% yield, without formation of the diethylated product. Although debenzylation of **15c** by catalytic hydrogenation under various conditions did not give satisfactory results, product **22** could be obtained by refluxing of **15c** in 48% hydrobromic acid in quantitative yield. Oxidation of **22** under the same conditions as described in the oxidation of **15b** afforded the desired *C*-nor-4,6-secocamptothecin **2** (mp 244-246°) in 75% yield.

None of the compounds **2-6** tested had any significant cytotoxic and topoisomerase I inhibition activities in *in vitro* assays. On the basis of these studies, it was clearly concluded that the *C*-ring, which induces the camptothecin molecule to a planar structure, might play an important role for marked antitumor activity.

Table 2

^{1}H NMR Spectral Data for 6-(2-Pyridinyl)-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-diones

Compound	1-H	4-H	5-H	3'-H	4'-H	5'-H	6'-H	Others
5	5.21 (d, 16) 5.63 (d, 16)		6.53 (*s*)	7.48 (d, 8)	7.83 (t, 8)	7.38 (dd, 5, 8)	8.72 (d, 5)	0.96 (t, 7.5, 3H) 1.80 (m, 2H) 3.48 (*s*, 3H) 3.65 (*s*, 1H)
6	5.42 (*s*)		[a]	7.45 (m)	7.87 (t, 8)	7.45 (m)	8.73 (d, 5)	3.45 (*s*, 3H) [a]
14	5.40 (*s*)	3.53 (*s*)	6.09 (*s*)	7.40 (m)	7.85 (t, 8)	7.40 (m)	8.72 (d, 5)	3.44 (*s*, 3H)
15a	5.25 (d, 17) 5.45 (d, 17)	3.40 (m)	6.08 (*s*)	7.40 (m)	7.85 (t, 8)	7.40 (m)	8.70 (d, 5)	0.97 (t, 7.5, 3H) 1.95 (m, 2H) 3.44 (*s*, 3H)
16a	5.34 (*s*)		6.10 (*s*)	7.45 (m)	7.85 (t, 8)	7.45 (m)	8.75 (d, 5)	0.78 (t, 7.5, 6H) 1.75 (m, 2H) 2.17 (m, 2H) 3.45 (*s*, 3H)

[a] 6.23, 6.41 and 6.75 (each *s*, each 1H, 5-H and/or vinyl-H_2).

Table 3

^{1}H NMR Spectral Data for 6-(2-Quinolinyl)-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-diones

Compound	δ (deuterioichloroform)/ppm (J/Hz) 1-H	4-H	5-H	3'-H	5'-H 6'-H 7'-H	4'-H 8'-H	Others
2	5.25 (d, 16) 5.68 (d, 16)		7.28 (*s*)	7.55 –	7.98 (m, 4H)	8.12 and/or 8.30 (each d, each 9)	1.03 (t, 7.5, 3H) 1.86 (m, 2H) 3.80 (br *s*, 1H)
3	5.22 (d, 15) 5.65 (d, 15)		6.67 (*s*)	7.55 –	7.90 (m, 4H)	8.12 and/or 8.32 (each d, each 9)	0.99 (t, 7.5, 3H) 1.83 (m, 2H) 3.55 (*s*, 3H) 3.62 (*s*, 1H)
4	5.46 (*s*)	[a]	[a]	7.53 –	7.92 (m, 4H)	8.15 and/or 8.35 (each d, each 9)	3.51 (*s*, 3H) [a]
15b	5.30 (d, 16) 5.50 (d, 16)	3.45 (br t, 7)	6.21 (*s*)	7.50 –	7.95 (m, 4H)	8.14 and/or 8.33 (each d, each 9)	1.01 (t, 7.5, 3H) 2.00 (m, 2H) 3.52 (*s*, 3H)
15c	5.29-5.65 (m) [b]	3.43 (t, 6)	6.15 (*s*)	7.17 (d, 8)	7.57-7.87 (m, 3H)	8.07 - 8.12 (m)	1.02 (t, 7.5, 3H) 2.00 (m, 2H) 5.29-5.65 (m, 4H) [b] 5.29-5.65 (m, 4H) [b] 7.05 (m, 3H)
16b	5.37 (*s*)		6.22 (*s*)	7.51 –	7.92 (m, 4H)	8.13 and/or 8.33 (each d, each 9)	0.80 (t, 7.5, 6H) 1.78 (m, 2H) 2.19 (m, 2H) 3.55 (*s*, 3H)
21a	5.42 (*s*)	3.58 (*s*)	6.23 (*s*)	7.52 –	7.92 (m, 4H)	8.12 and/or 8.33 (each d, each 9)	3.51 (*s*, 3H)
21b	5.45 (*s*)	3.57 (*s*)	6.17 (*s*)	7.15 (d, 8)	7.50 - 7.89 (m, 3H)	8.08-8.13 (m)	5.52 (*s*, 2H) 6.74 (d, 8, 2H) 7.00-7.10 (m, 3H)
21c	5.44 (*s*)	3.67 (*s*)	6.80 (*s*)	7.58 –	7.85 (m, 4H)	8.12 and/or 8.31 (each d, each 8)	
22	5.36 (d, 16) 5.55 (d, 16)	3.57 (t, 6)	6.80 (*s*)	7.61 –	7.95 (m, 4H)	8.15 and/or 8.35 (each d, each 8)	1.10 (t, 7.5, 3H) 2.10 (m, 2H)

[a] 6.26, 6.53 and 6.77 (each *s*, each 1H, 5-H and/or vinyl-H_2). [b] Overlapping Signals.

EXPERIMENTAL

The melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. The ir were recorded on a Shimadzu IR-435 spectrophotometer. The ^{1}H nmr were obtained in deuteriochloroform, unless otherwise stated, with a Varian Gemini-200 spectrometer; signals are given in ppm. Low-resolution and high-resolution mass (hrms) spectra were obtained on a Hitachi M-80 instrument. The C, H, N elemental analyses were performed on a Yanako CHN CORDER MT-3. For column chromatography, silica gel (Merck 7734 or 9385) was used. The physical constants and spectral data for compounds **2-6**, **14**, **15a-c**, **16a,b**, **21a-c**, and **22** are summarized in Tables 1, 2 and 3.

General Procedure for Preparation of Aminopropionates **9a,b**.

A solution of **8a** or **8b** (140 mmoles), formic acid (3.9 ml, 101 mmoles), and methylamine (3*N* benzene solution, 100 ml, 300 mmoles) in benzene (100 ml) was refluxed under a nitrogen stream with Dean Stark water separator. Then, ten 0.05 ml (0.001 mmole) portions of formic acid and ten 20 ml (60 mmoles) of methylamine (3*N* benzene solution) were added at 30 minutes intervals, and the mixture was refluxed for an additional 1 hour. After removal of excess of methylamine under reduced pressure, the benzene solution was washed with water and brine, dried (sodium sulfate), and evaporated. A mixture of the residual oil and sodium borohydride (7.26 g, 192 mmoles) in methanol (250 ml) was hydrogenated using a Skita apparatus under the initial pressure of 1.0 kg/cm^2 with 10% palladium on carbon (7.26 g) for 18 hours. After removal of the catalyst by filtration with the aid of Celite, the filtrate was evaporated. The residue was dissolved in ethyl acetate (100 ml), and the organic layer was washed with brine, dried (sodium sulfate) and evaporated to give almost pure **9a** or **9b** in nearly quantitative yield, respectively. This was subjected to the following reaction without further purification.

Ethyl 3-Methylamino-3-(2-pyridinyl)propionate (**9a**).

This compound was obtained as an oil; ir (neat): ν 3300 (NH), 1720 (C=O) cm^{-1}; ^1H nmr: δ 1.15 (t, J = 7.5 Hz, 3H, CH_2Me), 2.25 (s, 3H, NMe), 2.72 (d, J = 7.0 Hz, 2H, CH_2COOEt), 3.95-4.13 (m, 3H, CHN and CH_2Me), 7.1-7.4 (m, 2H, 3'- and 5'-H), 7.62 (t, J = 8.0 Hz, 1H, 4'-H), 8.55 (d, J = 5.0 Hz, 1H, 6'-H); ms: m/z 209 (M^+); hrms Calcd. for $C_{11}H_{17}N_2O_2$: 209.1290. Found: 209.1299 (M^+).

Ethyl 3-Methylamino-3-(2-quinolinyl)propionate (**9b**).

This compound was obtained as an oil; ir (neat): ν 3325 (NH), 1720 (C=O) cm^{-1}; ^1H nmr: δ 1.20 (t, J = 7.5 Hz, 3H, CH_2Me), 2.35 (s, 3H, NMe), 2.86 (d, J = 7.5 Hz, 2H, CH_2CO), 4.12 (q, J = 7.5 Hz, 2H, CH_2Me), 4.29 (t, J = 7.5 Hz, 1H, CHN), 7.52 (m, 2H, 3'- and 6'-H), 7.63-7.82 (m, 2H, 7'- and 5'-H), 8.02-8.15 (m, 2H, 4'- and 8'-H); ms: m/z 259 ($M^+ + 1$); hrms Calcd. for $C_{15}H_{19}N_2O_2$: 259.1446. Found: 259.1461 ($M^+ + 1$).

General Procedure for Preparation of Aminopropionates **9c,d**.

A solution of **8b** (4.86 g, 20 mmoles), formic acid (0.5 ml, 14 mmoles) and benzylamine (3.9 ml, 36 mmoles) in benzene (50 ml) was refluxed under nitrogen stream with Dean Stark water separator. Then, two 0.05 ml (0.001 mmole) portions of formic acid were added at 30 minutes intervals, and the mixture was refluxed for additional 1 hour. After cooling to room temperature, the reaction mixture was washed with water and brine, dried (sodium sulfate), and evaporated. A mixture of the residual oil and sodium borohydride (1.5 g, 40 mmoles) in methanol (100 ml) was hydrogenated using a Skita apparatus under an initial pressure of 1.0 kg/cm^2 with 10% palladium on carbon (1.5 g) for 18 hours. Workup as described for the preparation of **9a** gave the almost pure **9c** in nearly quantitative yield. This was subjected for the following reaction without further purification. Similarly, compound **9d** was obtained from **8c** (20 mmoles) and *p*-methoxyphenylmethylamine (36 mmoles) in nearly quantitative yield.

Ethyl 3-Benzylamino-3-(2-quinolinyl)propionate (**9c**).

This compound was obtained as an oil; ir (neat): ν 3400 (NH), 1720 (C=O) cm^{-1}; ^1H nmr: δ 1.17 (t, J = 7.5 Hz, 3H, CH_2Me), 2.88 (d, J = 7.5 Hz, 2H, CH_2CO), 3.69 (s, 2H, NCH_2), 4.10 (q, J = 7.5 Hz, 2H, CH_2Me), 4.43 (t, J = 7.5 Hz, 1H, CHN), 7.15-7.85 (m, 9H, 3', 5', 6', 7'-H and Ph-H), 8.10 (m, 2H, 4'- and 8'-H); ms: m/z 335 ($M^+ + 1$); hrms Calcd. for $C_{12}H_{23}N_2O_2$: 335.1758. Found: 335.1760 ($M^+ + 1$).

Ethyl 3-(4-Methoxybenzyl)amino-3-(2-quinolinyl)propionate (**9d**).

This compound was obtained as an oil; ir (neat): ν 3330 (NH), 1720 (C=O) cm^{-1}; ^1H nmr: δ 1.15 (t, J = 7.5 Hz, 3H, CH_2Me), 2.83 (d, J = 7.5 Hz, 2H, CH_2O), 3.59 (s, 2H, NCH_2), 3.77 (s, 3H, OMe), 4.08 (q, J = 7.5 Hz, 2H, CH_2Me), 4.37 (t, J = 7.5 Hz, CHN), 6.81 and 7.22 (each m, each 2H, 4-methoxyphenyl-H), 7.45-7.83 (m, 4H, 3'-, 5'-, 6'- and 7'-H), 8.03-8.12 (m, 2H, 4'- and 8'-H); ms: m/z 365 ($M^+ + 1$); hrms Calcd. for $C_{22}H_{25}N_2O_3$: 365.1865. Found: 365.1871 ($M^+ + 1$).

General Procedure for Preparation of Amides **10a-d**.

A solution of DCC (10.1 g, 48.8 mmoles) in dichloromethane (40 ml) was added to a solution of **9a** (9.23 g, 44.4 mmoles) and malonic acid monoethyl ester (6.45 g, 48.8 mmoles) in dichloromethane (100 ml) at 0°. After being stirred for 30 minutes at room temperature, the resulting insoluble precipitate was removed by filtration. The filtrate was extracted with 2*N* hydrochloric acid (100 ml x 2). The aqueous solution was basified with sodium bicarbonates and extracted with ethyl acetate. The extracts were washed with brine, dried (sodium sulfate) and evaporated. The residue was subjected to column chromatography [benzene-ethyl acetate (5:1)]. The ^1H nmr spectra clearly showed these compounds exist as a mixture of rotational isomers.

Ethyl 3-Oxo-3-{*N*-[2-ethoxycarbonyl-1-(2-pyridinyl)]ethyl-*N*-methyl}aminopropionate (**10**).

This compound was obtained in 84% yield as an oil; ir (neat): ν 1730, 1650 (C=O) cm^{-1}; ^1H nmr: δ 1.20 (m, 6H, CH_2Me x 2), 2.67 (s, 1H, NMe), 2.78 (s, 2H, NMe), 2.85 (m, 1H, C*H*HCH), 3.28 (dd, J = 15.0, 7.0 Hz, 2/3H, CH*H*CH), 3.45 (s, 4/3H, $NCOCH_2$), 3.52 (dd, J = 15.0, 7.0, 1/3H, CH*H*CH), 3.67 and 3.87 (each d, J = 14.0 Hz, each 1/3H, $NCOCH_2$), 4.12 (m, 4H, CH_2Me x 2), 5.45 and 6.30 (each t, J = 7.0 Hz, each 1H, CHN), 7.10-7.40 (m, 2H, 3'- and 5'-H), 7.63 (m, 1H, 4'-H), 8.49 (m, 1H, 6'-H); ms: m/z 322 (M^+); hrms Calcd. for $C_{16}H_{22}N_2O_5$: 322.1528. Found: 322.1532 (M^+).

Ethyl 3-Oxo-3-{*N*-[2-ethoxycarbonyl-1-(2-quinolinyl)]ethyl-*N*-methyl}aminopropionate (**10b**).

This compound was obtained in 74% yield as crystals, mp 82-84° (from ethyl acetate-hexane); ir (potassium bromide): ν 1740, 1730, 1645 (C=O) cm^{-1}; ^1H nmr: δ 1.23 (m, 6H, CH_2Me x 2), 2.69 (s, 1H, NMe), 2.77 (s, 2H, NMe), 2.92 (m, 1H, C*H*HCH), 3.40-4.00 (m, 3H, CH*H*CH and $NCOCH_2$), 4.15 (m, 4H, CH_2Me x 2), 5.62 (t, J = 7.0 Hz, 1/3H, CH_2CH), 6.52 (t, J = 7.0 Hz, 2/3H, CH_2CH), 7.40-8.20 (m, 6H, quinoline ring-H); ms: m/z 372 (M^+).

Anal. Calcd. for $C_{20}H_{24}N_2O_5$: C, 64.50; H, 6.50; N, 7.52. Found: C, 64.55; H, 6.49; N, 7.56.

Ethyl 3-Oxo-3-{*N*-[2-ethoxycarbonyl-1-(2-quinolinyl)]ethyl-*N*-benzyl}aminopropionate (**10c**).

This compound was obtained in 79% yield as an oil; ir (neat): ν 1725, 1640 (C=O) cm^{-1}; ^1H nmr: δ 1.20 (m, 6H, CH_2Me x 2), 2.85 (m, 1H, C*H*HCH), 3.40-4.80 (m, 9H, NCH_2, CH*H*CH, $NCOCH_2$, CH_2Me x 2), 5.70 (t, J = 7.0 Hz, 2/5H, CH_2CH), 6.62 (dd, J = 9.0, 6.0 Hz, 3/5H, CH_2CH), 7.00-8.10 (m, 11H, quinoline ring-H, Ph-H); ms: m/z 448 (M^+); hrms Calcd. for $C_{26}H_{28}N_2O_5$: 448.1996. Found: 448.2025 (M^+).

Ethyl 3-Oxo-3-{*N*-[2-ethoxycarbonyl-1-(2-quinolinyl)]ethyl-*N*-(4-methoxy)benzyl}aminopropionate (**10d**).

This compound was obtained in 83% yield as an oil; ir (neat): ν 1730, 1650 (C=O) cm^{-1}; ^1H nmr: δ 1.20 (m, 6H, CH_2Me x 2), 2.85 (m, 1H, C*H*HCH), 3.40-4.80 (m, 12H, NCH_2, CH*H*CH, $NCOCH_2$, CH_2Me x 2, OMe), 5.68 (t, J = 7.0 Hz, 1/2H, CH_2CH), 6.58 (dd, J = 9.0, 6.0 Hz, 1/2H, CH_2CH), 6.60-8.10 (m, 11H, quinoline ring-H, Ph-H); ms: m/z 479 ($M^+ + 1$); hrms Calcd. for $C_{27}H_{31}N_2O_6$: 479.2182. Found: 479.2168 ($M^+ + 1$).

Ethyl 4-Methoxy-1-methyl-2-oxo-6-(2-pyridinyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (**11**).

A solution of **10a** (3.22 g, 10 mmoles) in ethanol (20 ml) was added to a solution of sodium ethoxide [prepared from sodium (410 mg, 18 mmoles)] in ethanol (30 ml) at 0° under a nitrogen stream, and the mixture was stirred for 1 hour at room temperature. After the reaction mixture was neutralized by the addition of 10% hydrochloric acid, an ethereal diazomethane solution was

added until a yellow color persisted, and the mixture was stirred for additional 10 minutes. The mixture was condensed under reduced pressure, neutralized with saturated sodium hydrogen carbonate solution, and extracted with chloroform. The extract was washed with brine, dried (sodium sulfate), and evaporated *in vacuo*. The residual solid was recrystallized from 2-propanol to give **11** (2.17 g, 75%) as crystals, mp 151-155°; ir (potassium bromide): ν 1720, 1650 (C=O) cm^{-1}; ^1H nmr: δ 1.30 (t, J = 7.5 Hz, 3H, CH_2*Me*), 3.00 (s, 3H, NMe), 3.11 (d, J = 3.5 Hz, 1H, 5-H), 3.13 (d, J = 6.7 Hz, 1H, 5-H), 3.64 (s, 3H, OMe), 4.28 (q, J = 7.5 Hz, 2H, C*H*$_2$Me), 4.65 (dd, J = 6.7, 3.5 Hz, 1H, 6-H), 7.20 (m, 2H, 3'- and 5'-H), 7.69 (t, J = 8.0 Hz, 1H, 4'-H), 8.58 (d, J = 5.0 Hz, 1H, 6'-H); ms: m/z 290 (M^+).

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 62.15; H, 6.30; N, 9.48.

Di-*tert*-butyl [3-Ethoxycarbonyl-1-methyl-2-oxo-6-(2-pyridinyl)-1,2,5,6-tetrahydropyridin-4-yl]malonate (**12**).

A solution of di-*tert*-butyl malonate (3.24 g, 15 mmoles) in 1,4-dioxane (20 ml) was added to a suspension of 60% sodium hydride (0.7 g, 17.5 mmoles) in 1,4-dioxane (10 ml) at room temperature under a nitrogen stream. After being stirred for 30 minutes, **11** (2.9 g, 10 mmoles) was added in one-portion, and the mixture was refluxed for 1 hour. After evaporation of the solvent, the residue was quenched by the addition of cold 10% hydrochloric acid, then neutralized with saturated sodium hydrogen carbonate solution. The mixture was extracted with chloroform, and the extract was washed with brine, dried (sodium sulfate) and evaporated. The residue was subjected to column chromatography (chloroform) to give **12** (4.02 g, 85%), which was recrystallized from ethyl acetate to give crystals, mp 103-104°; ir (potassium bromide): ν 1740, 1710, 1650 (C=O) cm^{-1}; ^1H nmr: δ 1.12 (s, 9H, *t*-Bu), 1.30 (t, J = 7.5 Hz, 3H, CH_2*Me*), 1.42 (s, 9H, *t*-Bu), 2.96 (s, 3H, NMe), 2.98 (dd, J = 17.5, 2.5 Hz, 1H, 5-H), 3.34 (dd, J = 17.5, 7.5 Hz, 1H, 5-H), 4.26 [s, 2H, CH(CO$_2$-*t*-Bu)$_2$], 4.30 (q, J = 7.5 Hz, 2H, C*H*$_2$Me), 4.67 (dd, J = 7.5, 2.5 Hz, 1H, 6-H), 7.15 (m, 2H, 3'- and 5'-H), 7.64 (t, J = 8.0 Hz, 1H, 4'-H), 8.55 (d, J = 5.0 Hz, 6'-H); ms: m/z 474 (M^+).

Anal. Calcd. for $C_{25}H_{34}N_2O_7$: C, 63.27; H, 7.22; N, 5.90. Found: C, 63.08; H, 7.13; N, 5.91.

Di-*tert*-butyl [1,2-Dihydro-3-ethoxycarbonyl-1-methyl-2-oxo-6-(2-pyridinyl)pyridin-4-yl]malonate (**13**).

A solution of **12** (1.71 g, 3.6 mmoles) and DDQ (1.23 g, 5.4 mmoles) in benzene (20 ml) was refluxed for 1.5 hours. After cooling to room temperature, the precipitate was removed by filtration. The filtrate was washed with saturated sodium hydrogen carbonate solution and brine, dried (sodium sulfate) and evaporated. The residue was subjected to column chromatography [chloroform-methanol (50:1)] to give **13** (1.32 g, 78%), which was recrystallized from a mixture of ethyl acetate and hexane, mp 135-138°; ir (potassium bromide): ν 1745, 1725, 1649 (C=O) cm^{-1}; ^1H nmr: δ 1.32 (t, J = 7.5 Hz, 3H, CH_2*Me*), 1.37 (s, 18H, *t*-Bu x 2), 3.40 (s, 3H, NMe), 4.35 (q, J = 7.5 Hz, 2H, C*H*$_2$Me), 4.56 [s, 1H, CH(CO$_2$-*t*-Bu)$_2$], 6.40 (s, 1H, 5-H), 7.35 (m, 2H, 3'- and 5'-H), 7.76 (t, J = 8.0 Hz, 1H, 4'-H), 8.65 (d, J = 5.0 Hz, 1H, 6'-H); ms: m/z 472 (M^+).

Anal. Calcd. for $C_{25}H_{32}N_2O_7$: C, 63.54; H, 6.83; N, 5.93. Found: C, 63.30; H, 6.75; N, 6.00.

7-Methyl-6-(2-pyridinyl)-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-dione (**14**).

A 1.5 *M* solution of DIBAL (2.4 ml, 3.6 mmoles) in toluene was added to a solution of **13** (1,15 g, 2.4 mmoles) in DME (3 ml) at −78° under a nitrogen stream, and the mixture was stirred for 30 minutes at this temperature. The reaction was quenched by the addition of cold 10% hydrochloric acid, then neutralized with saturated sodium hydrogen carbonate solution. The mixture was diluted with chloroform (50 ml) and filtered through Celite. The filtrate was washed with brine, dried (sodium sulfate) and evaporated. To a solution of the residue in methanol (3 ml) was added sodium borohydride (355 mg, 9.6 mmoles), and the mixture was stirred for 2 hours at room temperature. After evaporation of the solvent *in vacuo*, trifluoroacetic acid (15 ml) was added to the residue, and the solution was stirred for 5 hours at room temperature, then concentrated *in vacuo*. The residue was neutralized with saturated sodium hydrogen carbonate solution and extracted with chloroform. The extract was washed with water, dried (sodium sulfate) and evaporated. The residual solid was recrystallized to give **14** (285 mg, 46%) as crystals.

4-Ethyl-7-methyl-6-(2-pyridinyl)-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-dione (**15a**) and 4,4-Diethyl-7-methyl-6-(2-pyridinyl)-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-dione (**16a**).

To a suspension of **14** (55 mg, 0.21 mmole) in dimethylformamide (1 ml) was added lithium hydride (17 mg, 2.1 mmoles) in one-portion and the mixture was stirred at room temperature for 30 minutes. After cooling to 0°, ethyl iodide (0.33 ml, 3 mmoles) was added dropwise over 15 minutes. After being stirred for 30 minutes at 0°, the reaction was quenched by the addition of cold 10% hydrochloric acid, then neutralized with saturated sodium hydrogen carbonate solution. The solution was extracted with dichloromethane (50 ml x 3). The extracts were washed with brine, dried (sodium sulfate) and evaporated. The residue was subjected to column chromatography (ethyl acetate) to give, in order of elution, **16a** (23.7 mg, 35%), **15a** (28.8 mg, 47%), and the starting material **14** (9.5 mg, 17% recovery).

4-Ethyl-4-hydroxy-7-methyl-6-(2-pyridinyl)-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-dione (**5**).

A stream of oxygen was bubbled into a suspension of **15a** (79 mg, 0.28 mmole), copper(II) acetate monohydrate (10.5 mg, 0.05 mmole) and triethylamine (50 mg, 0.5 mmole) in methanol (3 ml) at room temperature for 5 hours. After evaporation of the solvent *in vacuo*, the residue was agitated with 50% aqueous acetic acid (1 ml), then neutralized with saturated sodium hydrogen carbonate solution. The mixture was extracted with chloroform, and the extract was washed with brine, dried (sodium sulfate) and evaporated. The residue was subjected to column chromatography (ethyl acetate) to give **5** (50 mg, 60%).

7-Methyl-4-methylene-6-(2-pyridinyl)-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-dione (**6**).

A solution of **14** (26 mg, 0.1 mmole), *N*-methylanilinium trifluoroacetate (33 mg, 0.15 mmole) and paraformaldehyde (15 mg) in THF (3 ml) was refluxed for 6 hours. After evaporation of the solvent, the residue was extracted with chloroform. The extract was washed with brine, dried (sodium sulfate) and evaporated. The residue was subjected to column chromatography [chloroform-methanol (10:1)] to give **6** (20 mg, 74%).

General Procedure for Preparation of Dihydropyridones **17a,b,c**.

A solution of **10b-d** (15 mmoles) in ethanol (20 ml) was added to a solution of sodium ethoxide [prepared from sodium (449 mg, 19.5 mmoles)] at 0° under a nitrogen stream, and the mixture was stirred for 3 hours at room temperature. After evaporation of the solvent, the residue was acidified by the addition of cold 10% hydrochloric acid, then neutralized with saturated sodium hydrogen carbonate solution. The mixture was extracted with chloroform, and the extract was washed with brine, dried (sodium sulfate) and evaporated to give almost pure **17a-c** in nearly quantitative yield, respectively. These were used for the following reaction without purification.

Ethyl 4-Hydroxy-1-methyl-2-oxo-6-(2-quinolinyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (**17a**).

This compound was obtained as an oil; ir (neat): ν 1720, 1635 (C=O) cm^{-1}; ^1H nmr: δ 1.39 (t, J = 7.5 Hz, 3H, CH_2Me), 3.12 (s, 3H, NMe), 3.15-3.50 (m, 2H, 5-H_2), 4.34 (m, 2H, CH_2Me), 4.82 (dd, J = 7.5, 2.5 Hz, 1H, 6-H), 7.28 (d, J = 8.0 H, 1H, 3'-H), 7.47-7.82 (m, 3H, 5'-, 6'- and 7'-H), 7.80 (d, J = 8.0 Hz, 1H, 5'-H), 7.98-8.15 (m, 2H, 4'- and 8'-H); ms: m/z 326 (M^+); hrms Calcd. for $C_{18}H_{18}N_2O_4$: 326.1266. Found: 326.1268 (M^+).

Ethyl 1-Benzyl-4-hydroxy-2-oxo-6-(2-quinolinyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (**17b**).

This compound was obtained as an oil; ir (neat): ν 1720, 1640 (C=O) cm^{-1}; ^1H nmr: δ 1.40 (t, J = 7.5 Hz, 3H, CH_2Me), 3.21 (m, 2H, 5-H_2), 3.74 and 5.75 (each d, J = 14.0 Hz, each 1H, CH_2Ph), 4.38 (m, 2H, CH_2Me), 4.87 (br t, J = 3.0 Hz, 1H, 6-H), 7.30 (m, 6H, Ph-H, 3'H), 7.50-7.85 (m, 3H, 5'-, 6'- and 7'-H), 8.10 (m, 2H, 4'- and 8'-H); ms: m/z 402 (M^+); hrms Calcd. for $C_{24}H_{22}N_2O_4$: 402.1576. Found: 402.1580 (M^+).

Ethyl 4-Hydroxy-1-(4-methoxybenzyl)-2-oxo-6-(2-quinolinyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (**17c**).

This compound was obtained as an oil; ir (neat): 1720, 1640 (C=O) cm^{-1}; ^1H nmr: δ 1.48 (t, J = 7.5 Hz, 3H, CH_2Me), 3.18 (m, 2H, 5-H_2), 3.67 and 5.70 (each d, J = 15.0 Hz, each 1H, CH_2Ph), 3.73 (s, 3H, OMe), 4.37 (m, 2H, CH_2Me), 4.82 (m, 1H, 6-H), 6.80 and 7.20 (each d, J = 8.5 Hz, each 2H, Ph-H), 7.33 (d, J = 8.0 Hz, 1H, 3'-H), 7.51-7.88 (m, 3H, 5'-, 6'- and 7'-H), 8.08 (m, 2H, 4'- and 5'-H); ms: m/z 432 (M^+); hrms Calcd. for $C_{25}H_{24}N_2O_5$: 432.1684. Found: 432.1694 (M^+).

General Procedure for Preparation of Pyridones **18a,b,c**.

A solution of **17a** (12.3 g, 37.7 mmoles) and DDQ (10.3 g, 45 mmoles) in 1,4-dioxane (60 ml) was refluxed for 1.5 hours. After cooling to room temperature, the precipitate was removed by filtration. The filtrate was condensed *in vacuo*, and the residue was dissolved in chloroform (100 ml). The solution was washed with water and brine, dried (sodium sulfate) and evaporated. The residue was subjected to column chromatography (chloroform) to give **18a**.

Ethyl 1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-6-(2-quinolinyl)-pyridine-3-carboxylate (**18a**).

This compound was obtained in 86% yield as crystals, mp 154-156° (from ethanol); ir (potassium bromide): ν 1660, 1620 (C=O) cm^{-1}; ^1H nmr: δ 1.40 (t, J = 7.5 Hz, 3H, CH_2Me), 3.35 (s, 3H, NMe), 4.42 (q, J = 7.5 Hz, 2H, CH_2Me), 6.07 (s, 1H, 5-H), 7.45-7.90 (m, 4H, 3'-, 5'-, 6'- and 7'-H), 8.08 (d, J = 8.0 Hz, 1H, 8'-H), 8.28 (d, J = 8.0 Hz, 1H, 4'-H); ms: m/z 324 (M^+).

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.63; H, 4.99; N, 8.55.

Ethyl 1-Benzyl-1,2-dihydro-4-hydroxy-2-oxo-6-(2-quinolinyl)pyridine-3-carboxylate (**18b**).

This compound was obtained in 80% yield as an oil; ir (neat): ν 1655, 1630 (C=O) cm^{-1}; ^1H nmr: δ 1.45 (t, J = 7.5 Hz, 3H, CH_2Me), 4.49 (q, J = 7.5 Hz, 2H, CH_2Me), 5.45 (s, 2H, NCH_2), 6.06 (s, 1H, 5-H), 6.72-7.01 (m, 5H, Ph-H), 7.13 (d, J = 8.0 Hz, 1H, 3'-H), 7.58-7.85 (m, 3H, 5'-, 6'- and 7'-H), 8.07 (m, 2H, 4'- and 8'-H); ms: m/z 400 (M^+); hrms Calcd. for $C_{24}H_{20}N_2O_4$: 400.1423. Found: 400.1421 (M^+).

Ethyl 1,2-Dihydro-4-hydroxy-1-(4-methoxybenzyl)-2-oxo-6-(2-quinolinyl)pyridine-3-carboxylate (**18c**).

This compound was obtained in 81% yield as an oil; ir (neat): ν 1655, 1630 (C=O) cm^{-1}; ^1H nmr: δ 1.43 (t, J = 7.5 Hz, 3H, CH_2Me), 3.64 (s, 3H, OMe), 4.46 (q, J = 7.5 Hz, 2H, CH_2Me), 5.38 (s, 2H, NCH_2), 6.02 (s, 1H, 5-H), 6.52 and 6.65 (each d, J = 8.0 Hz, each 2H, Ph-H), 7.13 (d, J = 8.0 Hz, 1H, 3'-H), 7.58-7.85 (m, 5'-, 6'- and 7'-H), 8.09 (d, J = 8.0 Hz, 2H, 4'- and 8'-H); ms: m/z 430 (M^+); hrms Calcd. for $C_{25}H_{22}N_2O_5$: 430.1529. Found: 430.1521 (M^+).

General Procedure for Preparation of Methoxypyridones **19a,b,c**.

A suspension of **18a** (9.02 g, 27.8 mmoles), dimethyl sulfate (7.01 g, 55.7 mmoles) and potassium carbonate (7.68 g, 55.7 mmoles) in acetone (60 ml) was refluxed with vigorous stirring for 1 hour. The insoluble material was removed by filtration, and the filtrate was evaporated. The residue was dissolved in chloroform, and the solution was washed in turn with water, 10% ammonium hydroxide solution, brine and water, then dried (sodium sulfate). After evaporation of the solvent, the residue was recrystallized to give **19a**.

Ethyl 1,2-Dihydro-4-methoxy-1-methyl-2-oxo-6-(2-quinolinyl)pyridine-3-carboxylate (**19a**).

This compound was obtained in 77% yield as crystals, mp 146-147° (from ethyl acetate); ir (potassium bromide): ν 1730, 1630 (C=O) cm^{-1}; ^1H nmr: δ 1.37 (t, J = 7.5 Hz, 3H, CH_2Me), 3.41 (s, 3H, NMe), 3.87 (s, 3H, OMe), 4.38 (q, J = 7.5 Hz, 2H, CH_2Me), 6.18 (s, 1H, 5-H), 7.45-7.82 (m, 4H, 3'-, 5'-, 6'- and 7'-H), 8.13 (d, J = 8.0 Hz, 1H, 8'-H), 8.30 (d, J = 9.0 Hz, 1H, 4'-H); ms: m/z 338 (M^+).

Anal. Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.37; H, 5.35; N, 8.37.

Ethyl 1-Benzyl-1,2-dihydro-4-methoxy-2-oxo-6-(2-quinolinyl)pyridine-3-carboxylate (**19b**).

This compound was obtained in 85% as crystals, mp 178-180° (from a mixture of ethyl acetate-hexane); ir (potassium bromide): ν 1720, 1640 (C=O) cm^{-1}; ^1H nmr: δ 1.38 (t, J = 7.5 Hz, 3H, CH_2Me), 3.88 (s, 3H, OMe), 4.40 (q, J = 7.5 Hz, 2H, CH_2Me), 5.45 (s, 2H, NCH_2), 6.14 (s, 1H, 5-H), 6.73-7.05 (m, 7H, Ph-H and 3'-H), 7.58-7.88 (m, 3H, 5'-, 6'- and 7'-H), 8.09 (m, 2H, 4'- and 8'-H); ms: m/z 414 (M^+).

Anal. Calcd. for $C_{25}H_{22}N_2O_4$: C, 72.45; H, 5.35; N, 6.76. Found:

C, 72.42; H, 5.41; N, 6.64.

Ethyl 1,2-Dihydro-4-methoxy-1-(4-methoxybenzyl)-2-oxo-6-(2-quinolinyl)pyridine-3-carboxylate (**19c**).

This compound was obtained in 90% yield as crystals, mp 154-156° (from 2-propanol); ir (potassium bromide): ν 1720, 1635 (C=O) cm^{-1}; ^1H nmr: δ 1.38 (t, J = 7.0 Hz, 3H, CH_2Me), 3.66 (s, 3H, PhOMe), 3.86 (s, 3H, 4-OMe), 4.40 (q, J = 7.0 Hz, 2H, CH_2Me), 5.37 (s, 2H, NCH_2), 6.09 (s, 1H, 5-H), 6.52 and 6.65 (each d, J = 9.0 Hz, each 2H, Ph-H), 7.11 (d, J = 8.0 Hz, 1H, 3'-H), 7.60-7.88 (m, 5'-, 6'- and 7'-H), 8.12 (m, 2H, 4'- and 8'-H); ms: m/z 444 (M^+).

Anal. Calcd. for $C_{26}H_{24}N_2O_5$: C, 70.25; H, 5.44; N, 6.30. Found: C, 70.49; H, 5.48; N, 6.23.

General Procedure for Preparation of Pyridones **20a,b,c**.

A solution of di-*tert*-butyl malonate (2.33 g, 10.8 mmoles) in 1,4-dioxane (8 ml) was added to a suspension of 60% sodium hydride (431 mg, 10.8 mmoles) in 1,4-dioxanes (5 ml) at room temperature under a stream of nitrogen, and the mixture was stirred for 30 minutes. A solution of **19a** (18.2 g, 5.4 mmoles) in 1,4-dioxane (8 ml) was then added, the reaction mixture was refluxed for 3.5 hours with stirring. After evaporation of the solvent, the residue was quenched by the addition of cold 10% hydrochloric acid, then neutralized with saturated sodium hydrogen carbonate solution, and extracted with chloroform. The extract was washed with brine, dried (sodium sulfate), and evaporated. The residue was subjected to column chromatography [benzene-ethyl acetate (10:1)] to give **20a**.

Di-*tert*-butyl [1,2-Dihydro-3-ethoxycarbonyl-1-methyl-2-oxo-6-(2-quinolinyl)pyridin-4-yl]malonate (**20a**).

This compound was obtained in 62% yield as crystals, mp 125-126° (from a mixture of ethyl acetate and hexane); ir (potassium bromide): ν 1730, 1720, 1640 (C=O) cm^{-1}; ^1H nmr: δ 1.35 (t, J = 7.5 Hz, 3H, CH_2Me), 1.42 (s, 18H, *t*-Bu x 2), 3.54 (s, 3H, NMe), 4.42 (q, J = 7.5 Hz, 2H, CH_2Me), 4.65 [s, 1H, $CH(CO_2$-*t*-$Bu)_2$], 6.59 (s, 1H, 5-H), 7.52-7.90 (m, 4H, 3'-, 5'-, 6'- and 7'-H), 8.08 (d, J = 8.0 Hz, 1H, 8'-H), 8.30 (d, J = 9.0 Hz, 1H, 4'-H); ms: m/z 522 (M^+).

Anal. Calcd. for $C_{29}H_{34}N_2O_7$: C, 66.65; H, 6.56; N, 5.36. Found: C, 66.47; H, 6.57; N, 5.49.

Di-*tert*-butyl [1-Benzyl-1,2-dihydro-3-ethoxycarbonyl-2-oxo-6-(2-quinolinyl)pyridin-4-yl]malonate (**20b**).

This compound was obtained in 77% yield as crystals, mp 169-171° (from ethanol); ir (potassium bromide): ν 1740, 1720, 1650 (C=O) cm^{-1}; ^1H nmr: δ 1.40 (t, J = 7.5 Hz, 3H, CH_2Me), 1.43 (s, 18H, *t*-Bu x 2), 4.42 (q, J = 7.5 Hz, 2H, CH_2Me), 4.67 [s, 1H, $CH(CO_2$-*t*-$Bu)_2$] 5.62 (s, 2H, NCH_2), 6.54 (s, 1H, 5-H), 6.75-7.02 (m, 5H, Ph-H), 7.19 (d, J = 8.0 Hz, 1H, 3'-H), 7.57-7.88 (m, 3H, 5'-, 6'- and 7'-H), 8.08 (d, J = 8.0 Hz, 2H, 4'- and 8'-H); ms: m/z 598 (M^+).

Anal. Calcd. for $C_{35}H_{38}N_2O_7$: C, 70.21; H, 6.40; N, 4.68. Found: C, 70.05; H, 6.25; N, 4.67.

Di-*tert*-butyl [1,2-Dihydro-3-ethoxycarbonyl-1-(4-methoxybenzyl)-2-oxo-6-(2-quinolinyl)pyridin-4-yl]malonate (**20c**).

This compound was obtained in 68% yield as crystals, mp 146-148° (from a mixture of ethanol-ether); ir (potassium bromide): ν 1720, 1650 (C=O) cm^{-1}; ^1H nmr: 1.40 (t, J = 7.0 Hz, 3H, CH_2Me), 1.42 (s, 18H, *t*-Bu x 2), 3.67 (s, 3H, OMe), 4.42 (q, J = 7.0 Hz, 2H, CH_2Me), 4.65 [s, 1H, $CH(CO_2$-*t*-$Bu)_2$], 5.55 (s, 2H, NCH_2), 6.51 (s, 1H, 5-H), 6.53 and 6.68 (each d, J = 9.0 Hz, each 2H, Ph-H), 7.20 (d, J = 8.0 Hz, 1H, 3'-H), 7.55-7.86 (m, 5'-, 6'- and 7'-H), 8.09 (m, 2H, 4'- and 8'-H); ms: m/z 628 (M^+).

Anal. Calcd. for $C_{36}H_{40}N_2O_8$: C, 68.77; H, 6.41; N, 4.46. Found: C, 68.68; H, 6.36; N, 4.40.

General Procedure for Preparation of Lactones **21a,b,c**.

A 1.5 *M* solution of DIBAL (3.3 ml, 5 mmoles) in toluene was added to a solution of **20a** (1.74 g, 3.3 mmoles) in DME 12 ml) at −78° under a nitrogen stream, and the mixture was stirred for 20 minutes at this temperature. The reaction was quenched by the addition of 10% hydrochloric acid, and then neutralized with saturated sodium hydrogen carbonate solution. The reaction mixture diluted with chloroform was filtered through Celite, and the filtrate was washed with brine, dried (sodium sulfate) and evaporated. To a solution of the residue in methanol (12 ml) was added sodium borohydride (506 mg, 13.3 mmoles). After being stirred for 20 minutes, the solvent was evaporated and trifluoroacetic acid was added to the residue. After the mixture was stirred for for 1 hour, trifluoroacetic acid was evaporated, neutralized with saturated sodium hydrogen carbonate solution, and extracted with chloroform. The extract was washed with brine, dried (sodium sulfate) and evaporated. The residue was recrystallized to give 7-Methyl-6-(2-quinolinyl)-1*H*-pyrido[3,4-*c*]pyridine-3,8(4*H*,7*H*)-dione **21a** (632 mg, 62%).

Similar treatments of **20b** and **20c** gave 7-benzyl-6-(2-quinolinyl)-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-dione (**21b**) (85%) and 6-(2-quinolinyl)-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-dione (**21c**) (73%).

4-Ethyl-7-methyl-6-(2-quinolinyl)-1*H*-pyrano[3,4-*c*]pyridine-3,8-(4*H*,7*H*)-dione (**15b**) and 4,4-Diethyl-7-methyl-6-(2-quinolinyl)-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*.7*H*)-dione (**16b**).

By the same procedure as that described for the preparation of **15a** and **16a**, the crude product which was obtained from **21a** (306 mg, 1 mmole), ethyl iodide (312 mg, 2 mmoles) and lithium hydride (40 mg, 5 mmoles) was subjected to column chromatography [benzene-ethyl acetate (5:1)] to give, in order of elution **16b** (17 mg, 5%) and **15b** (90 mg, 27%), and starting material **21a** (172 mg, 56% recovery).

7-Benzyl-4-ethyl-6-(2-quinolinyl)-1*H*-pyrano[3,4-*c*]pyridine-3,8-(4*H*,7*H*)-dione (**15c**).

By the same procedure as that described for ethylation of **14**, the crude product which was obtained from **21b** (76 mg, 0.2 mmole), ethyl iodide (624 mg, 4 mmoles) and lithium hydride (16 mg, 2 mmoles) was subjected to column chromatography (chloroform) to give, in order of elution, **15c** (37 mg, 45%) and the starting material **21b** (35 mg, 46%).

4-Ethyl-6-(2-quinolinyl)-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-dione (**22**).

A solution of **15c** (25.4 g, 0.062 mmole) in 47% hydrobromic acid (10 ml) was refluxed for 30 minutes. After evaporation of hydrobromic acid *in vacuo*, the residue was neutralized with saturated sodium hydrogen carbonate solution, and extracted with chloroform. The exact was washed with brine, dried (sodium sulfate) and evaporated. The residue was subjected to column chromatography [chloroform-ethyl acetate (10:1)] to give **22** (20 mg, 100%).

4-Ethyl-4-hydroxy-7-methyl-6-(2-quinolinyl)-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-dione (**3**).

By the same procedure as that described for the preparation of **5**, the crude product which was obtained from **15b** (75 mg, 0.22 mmole), triethylamine (40 mg, 0.4 mmole) and copper(II) acetate monohydrate (8 mg, 0.04 mmole) was subjected to column chromatography [chloroform-ethyl acetate (10:1)] to give **3** (45 mg, 57%).

4-Ethyl-4-hydroxy-6-(2-quinolinyl)-1*H*-pyrano[3,4-*c*]pyridine-3,8-(4*H*,7*H*)-dione (**2**).

By the same procedure as that described for the preparation of **5**, the crude product which was obtained from **22** (39 mg, 0.12 mmole), triethylamine (22 mg, 0.22 mmole), and copper(II) acetate monohydrate (44 mg, 0.02 mmole) was subjected to column chromatography [chloroform-ethyl acetate (10:1)] to give **2** (31 mg, 75%).

7-Methyl-4-methylene-6-(2-quinolinyl)-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-dione (**4**).

By the same procedure as that described for the preparation of **6**, the crude product which was obtained from **21a** (31 mg, 0.1 mmole), paraformaldehyde (18 mg, 0.6 mmoles), and *N*-methylanilinium trifluoroacetate (44 mg, 0.2 mmole) was recrystallized to give **4** (27 mg, 85%).

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