A Facile Synthesis of Substituted 5,11-Dihydro[1]benzoxepino[3,4-*b*]pyridines

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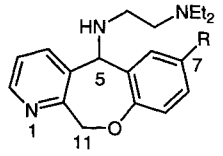
Received 22 March 1996

5-Amino-5,11-dihydro[1]benzoxepino[3,4-*b*]pyridines (**1**) show antiulcer and antiarrhythmic activity. An efficient method for the preparation of a key intermediate, furo[3,4-*b*]pyridin-5(7*H*)-one (**4**), and the facile synthesis of **1** were described. The reduction of quinolinic anhydride (**5**) with sodium borohydride in the presence of acetic acid regioselectively gave the lactone **4**. Lactone **4** was then reacted with substituted phenols under basic conditions and the resultant products, 2-(phenoxymethyl)-3-pyridinecarboxylic acids (**3**), underwent Friedel-Crafts cyclizations to produce the 5,11-dihydro[1]benzoxepino[3,4-*b*]pyridin-5-ones (**2**). Compounds **2** were then converted to imines with amines and successively reduced with zinc in acetic acid to the desired compounds **1**.

Some 5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine derivatives have been reported to show various pharmacological activities.[1–3] Among them, 5-{[2-(diethylamino)ethyl]amino}-5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine (**1a**) has a highly potent antiulcer activity,[2] and the 7-methoxy substituted compound, 5-{[2-(diethylamino)ethyl]amino}-7-methoxy-5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine (**1b**), has antiarrhythmic activity (Figure 1).[3] These compounds have been derived from the corresponding C–5 carbonyl compounds, 5,11-dihydro[1]benzoxepino[3,4-*b*]pyridin-5-ones (**2**).

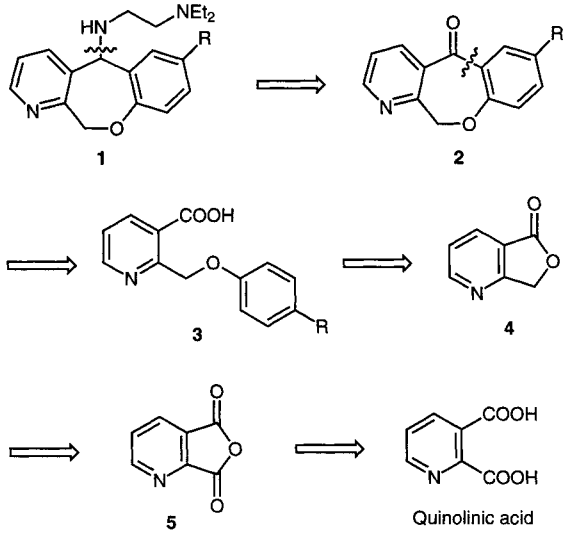


1a: R = H
1b: R = OMe

Figure 1

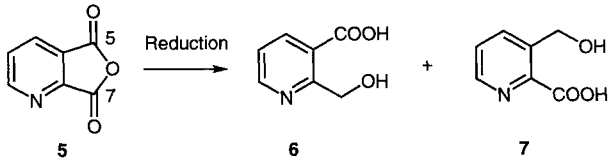
The synthetic methods of **2** have already been reported.[1–4] In these methods, however, the pyridine nucleus was constructed during the later stage of the tricyclic system synthesis and many complicated steps were involved. For example, the synthesis of **2** from ethyl chloroacetoacetate using a 4-substituted phenol required 6 steps, 4 steps of which were for the construction of the pyridine nucleus,[2,3] another one from acetyl chloride, and 4-substituted anisole also needed 6 steps and the pyridine nucleus was made during the last stage.[4] A more convenient synthetic method of **2** was desired for the commercial scale synthesis of pharmaceutically useful 5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine derivatives. We accomplished the synthetic route of **2** from quinolinic acid which initially has a pyridine moiety and is commercially available (Scheme 1).

The efforts to synthesize furo[3,4-*b*]pyridin-5(7*H*)-one (**4**) from quinolinic acid derivatives have been made.[5–9] The selective reduction of 5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione (quinolinimide) by treatment with sodium borohydride in the presence of magnesium perchlorate and



Scheme 1

the following reactions were reported to give **4** by Goto and co-workers.[8] They required many steps and the yield of **4** (36% from **5**) was still low.[8] On the other hand, the reduction of quinolinic anhydride (**5**) readily derived from quinolinic acid is known, but the reduction of **5** using lithium aluminum hydride[6] or catalytic hydrogenation[7] gave the mixture of 2-hydroxymethyl-3-pyridinecarboxylic acid (**6**) and its regioisomer **7** in 25% and 8% yields, and the ratio of **6**/**7** was 2.0 and 0.15, respectively. We sought to screen reducing agents and solvents for the regioselective reduction of **5**.



Scheme 2

The reduction of **5** with sodium triacetoxyborohydride or sodium cyanoborohydride in tetrahydrofuran, and zinc in a mixture of tetrahydrofuran and acetic acid showed superior selectivity (Table 1, entries 5–7). With regard to the yield of **6**, these reduction conditions were inferior to sodium borohydride in tetrahydrofuran or dimethoxyethane, and lithium borohydride in tetrahydrofuran (Table 1, entries 2, 3 and 8). Both yield and selectivity of reduction of **5** with sodium borohydride in *tert*-butyl alcohol were quite low (Table 1, entry 9). Instead of using sodium triacetoxyborohydride or sodium

Table 1. Reduction of **5**,[a] Effects of Reducing Agent and Solvent

Entry	Reducing agent	Solvent	Yield of **6** (%)	Ratio (**6**/**7**)[b]
1	$LiAlH_4$	THF	34	2.7
2	$NaBH_4$	THF	42	3.0
3	$LiBH_4$	THF	39	3.9
4	$NaB(OMe)_3H$	THF	21[c]	3.2
5	$NaB(OAc)_3H$	THF	30	6.8
6	$NaCNBH_3$	THF	18[d]	6.5
7	Zn	THF-HOAc (1:1)	24	8.2
8	$NaBH_4$	DME	43	2.7
9	$NaBH_4$	*t*-BuOH	5	0.9

[a] Reaction conditions: compound **5** (0.5 g) in 5 mL of solvent was treated with 1 molar equivalent of reducing agent at r.t. for 12 h.
[b] Determined by HPLC analysis.
[c] Two types of quinolinic acid monomethyl esters were obtained as major products.
[d] Complicated mixtures.

cyanoborohydride, we studied some additives to the reduction of **5** with sodium borohydride or lithium borohydride in tetrahydrofuran for improving both the yield and regioselectivity (Table 2).

The higher regioselectivity was achieved in the presence of acetic acid, trifluoroacetic acid or zinc chloride as additives (Table 2, entries 4–8). Furthermore, the yields of **6** moderately increased. In the presence of these additives, the pyridine nucleus of **5** might be partially protonated or chelated and the 7-carbonyl group would be more activated for an attack by the hydride ion in comparison with the 5-carbonyl group, therefore, compound **6** would be preferentially produced. From the viewpoint of material prices and ease of disposal treatment, sodium borohydride and acetic acid were selected for a commercial scale synthesis (Table 2, entry 4).

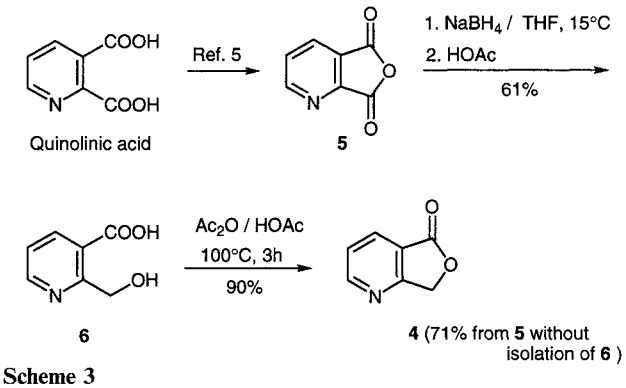
As a result of optimizing the amount of sodium borohydride and acetic acid, the yield of **6** from **5** was raised to 61% (1 molar equivalent of sodium borohydride and 1.5–2.0 molar equivalents of acetic acid).

Table 2. Reduction of **5**,[a] Effects of Reducing Agent and Additive

Entry	Reducing agent	Additive	Yield of **6** (%)	Ratio (**6**/**7**)[b]
1	$NaBH_4$	None	42	3.0
2	$NaBH_4$	DMF	32	1.3
3	$NaBH_4$	MeOH	–[c]	1.9
4	$NaBH_4$	HOAc	49	8.9
5	$NaBH_4$	$ZnCl_2$	65	8.7
6	$NaBH_4$	CF_3CO_2H	62	11.7
7	$LiBH_4$	HOAc	55	6.3
8	$LiBH_4$	$ZnCl_2$	59	8.0

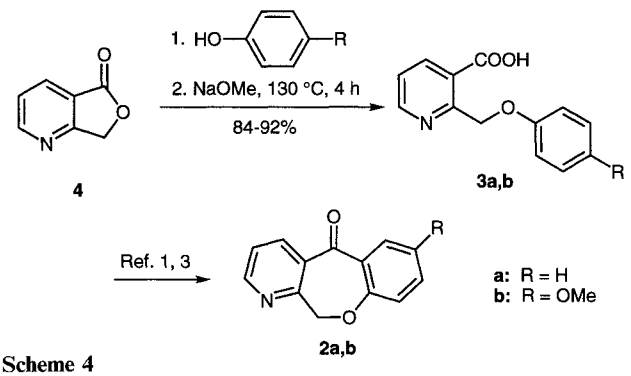
[a] Reaction conditions: compound **5** (0.5 g) in THF (5 mL) was treated with 1 molar equivalent of reducing agent and 1 molar equivalent of additive at r.t. for 12 h.
[b] Determined by HPLC analysis.
[c] Two types of quinolinic acid monomethyl esters were obtained as major products.

The lactonization of **6** was executed by the treatment with acetic anhydride and the key compound **4** was obtained in 90% yield. The lactone **4** could also be obtained in a one-pot reaction from **5** without the isolation of **6** as follows: concentration of the reductant mixture of **5** and heating the residue with acetic anhydride gave **4** in 71% yield.



Scheme 3

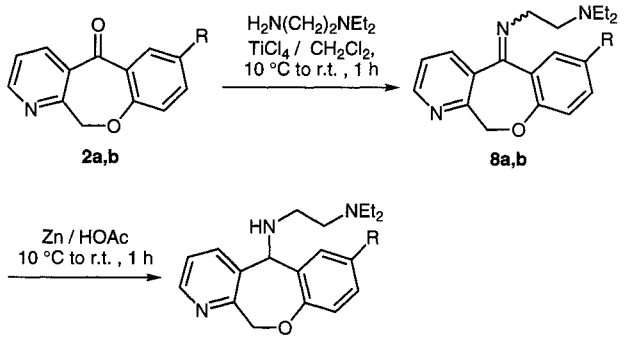
The base-catalyzed reaction of phthalide with substituted phenols has been known to afford the corresponding ring-opening products in 60–80% yield.[9] We carried out the reaction of **4** with substituted phenols using sodium methoxide (the molar ratio was 1 : 2 : 1.2) under the similar conditions adapted in the case of phthalide.[9] With phenol, however, 2-(phenoxymethyl)-3-pyridinecarboxylic acid (**3a**) was obtained in only 46% yield and the starting material **4** was recovered. It was suggested that **3a** was in equilibrium with **4** and phenol under the basic conditions, therefore, the use of an excess amount of substituted phenols was expected to give compound **3** in high yield. Actually, the reaction of **4** and substituted phenols with sodium methoxide (the molar ratio was 1 : 5 : 2.4) gave **3a** and **3b** in 84% and 92% yields, respectively. The following cyclization of **3a** and **3b** gave the corresponding ketones **2** according to the already reported methods.[1,3]



Scheme 4

Primarily, compounds **1a** and **1b** were prepared from **2** by the reduction of the 5-carbonyl group with sodium borohydride, the chlorination of the alcohol with thionyl chloride and the substitution of the resultant chloride

with *N,N*-diethylethylenediamine.[2,3] Avoiding the tedious steps, we used the reductive amination method[3] and optimized the reaction conditions. Condensation of the ketones **2** with *N,N*-diethylethylenediamine was carried out in the presence of titanium tetrachloride in dichloromethane, and the reduction of the resultant imines (**8a,b**; not isolated) was practiced by treatment with zinc in acetic acid. Compounds **1a** and **1b** were isolated as the trihydrochlorides in yields of 71% and 83% from **2**, respectively (Scheme 5).



2a,b **8a,b**

1a R = H (trihydrochloride; 71% from **2a**)
b R = OMe (trihydrochloride; 83% from **2b**)

Scheme 5

In summary, the regioselective reduction of quinolinic anhydride **5** with sodium borohydride in the presence of acetic acid, followed by lactonization with acetic anhydride gave **4** in high yield. The base-catalyzed reaction of **4** with an excess of substituted phenols gave **3a,b** in high yields. This is a facile synthesis of **3** from quinolinic acid. After the Friedel-Crafts cyclization of **3a,b**, the resultant ketones **2a,b** were converted to the corresponding imines **8a,b** upon treatment with an amine in the presence of titanium tetrachloride in dichloromethane. The reduction of the imines with zinc in acetic acid gave **1a,b** in high yields. These methods were suitable for the commercial scale synthesis of **1a** and **1b**. Both compounds have been synthesized on a multi kilogram scale.

Melting points were determined using a Mettler FP62 point instrument and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-300 spectrometer using TMS as the internal reference. Mass spectra were recorded on a Hitachi M-80B mass spectrometer. The ratio of compounds **6** and **7** was determined by HPLC analysis [column: YMC Pack A-312 ODS 6 × 150 mm; mobile phase: MeOH-H_2O(1:9); 1.0 g/L sodium octanesulfonate; 13.7 g/L citric acid; pH 2.0 adjusted with 85% H_3PO_4; 1.0 mL/min flow rate; detection: UV 254 nm]. Quinolinic anhydride **(5)** was prepared from quinolinic acid according to the reported procedure.[5] Quinolinic acid was obtained from Aldrich. Diaion SK1B (a strongly acidic gel-type resin) was obtained from Mitsubishi Chemical Co. The spectroscopic properties (IR and ^{1}H NMR) and retention times on HPLC analysis of our synthetic **1a,b** and **2a,b** were identical with those of **1a,b** and **2a,b** which were synthesized using reported procedures.[2,3]

Reduction of Quinolinic Anhydride (5):
To a solution of **5** (44.7 g, 0.30 mol) in THF (350 mL) was added $NaBH_4$ (11.3 g, 0.30 mol) at 15 °C under N_2, then HOAc (36.0 g, 0.60 mol) was added dropwise along with evolving H_2 gas at 15 °C under N_2. After stirring at 15 °C for 4 h under N_2, the mixture was concentrated under reduced pressure. The residue was dissolved in H_2O (300 mL) and the pH of the solution was adjusted to 1.5 with 4 N H_2SO_4 (160 mL). The mixture was charged onto an ion-exchange resin (700 mL, Diaion SK1B, H^+ type), eluted with 1N NH_4OH, and the fractions containing compound **6** were concentrated under reduced pressure. The residue was recrystallized from EtOH to afford **6** as crystals; yield: 27.8 g (61%).

^{1}H NMR (DMSO-d_6): δ = 4.68 (s, 2H), 7.31 (dd, 1H, J = 4.7, 7.7 Hz), 8.14 (dd, 1H, J = 1.8, 7.7 Hz), 8.45 (dd, 1H, J = 1.8, 4.7 Hz).

HRMS: *m/z* calc. for $C_7H_7NO_3$: 153.0424, found: 153.0353.

Furo[3,4-*b*]pyridin-5(7*H*)-one (4):
A solution of **6** (23.0 g, 0.15 mol) in HOAc (100 mL) and Ac_2O (43 mL) was stirred at 100 °C for 3 h. The mixture was concentrated under reduced pressure and to the residue were added H_2O (300 mL) and NaCl (60 g). The water layer was extracted with $CHCl_3$ (2 × 300 mL). The combined $CHCl_3$ extracts were concentrated under reduced pressure and the residue was recrystallized from *i*-PrOH to afford **4** as crystals (18.3 g, 90%); mp 141 °C (Lit.[7] mp 141–142 °C from MeOH).

^{1}H NMR ($CDCl_3$): δ = 5.35 (s, 2H), 7.51 (dd, 1H, J = 4.7, 7.7 Hz), 8.22 (dd, 1H, J = 1.8, 7.7 Hz), 8.88 (dd, 1H, J = 1.8, 4.7 Hz).

HRMS: *m/z* calc. for $C_7H_7NO_2$: 135.0320, found: 135.0348.

One-Pot Synthesis of Furo[3,4-*b*]pyridin-5(7*H*)-one (4):
To a solution of **5** (30.0 g, 0.20 mol) in THF (200 mL) was added $NaBH_4$ (7.5 g, 0.20 mol) at 15 °C under N_2, then HOAc (24.0 g, 0.40 mol) was added dropwise along with evolving H_2 gas at 15 °C under N_2. After being stirred at 15 °C for 4 h under N_2, the mixture was concentrated under reduced pressure. HOAc (80 mL) and Ac_2O (80 mL) were added to the residue and the solution was stirred at 100 °C for 3 h. The mixture was concentrated under reduced pressure and to the residue were added H_2O (200 mL) and NaCl (40 g). The water layer was extracted with $CHCl_3$ (2 × 200 mL). The combined $CHCl_3$ extracts were concentrated under reduced pressure and the residue was recrystallized from *i*-PrOH to afford **4**; yield: 19.2 g (71%).

2-(Phenoxymethyl)-3-pyridinecarboxylic Acid (3a):
A mixture of **4** (8.4 g, 0.062 mol) and phenol (29.2 g, 0.31 mol) was heated to 130 °C under N_2, then NaOMe (28% methanolic solution, 24.0 g, 0.12 mol) was added dropwise to the mixture at 130 °C with distillation of the MeOH. The mixture was stirred at 130 °C for 4 h, then the mixture was cooled to 80 °C and the pH of the solution was adjusted to 5.0 with 1M HCl (124 mL) at 80 °C. The mixture was cooled to r.t. and concentrated to 50 mL under reduced pressure. H_2O (200 mL) was added dropwise to the concentrate to afford **3a** as crystals; yield: 11.9 g (84%); mp 213 °C (Lit.[2] mp 212–213 °C from EtOH-H_2O).

^{1}H NMR (DMSO-d_6): δ = 5.47 (s, 2H), 6.91–7.02 (m, 3H), 7.24–7.34 (m, 2H), 7.54 (dd, 1H, J = 4.8, 7.8 Hz), 8.24 (dd, 1H, J = 1.7, 7.8 Hz), 8.73 (dd, 1H, J = 1.7, 4.8 Hz).

HRMS: *m/z* calc. for $C_{13}H_{11}NO_3$: 229.0739, found: 229.0705.

2-(4-Methoxyphenoxymethyl)-3-pyridinecarboxylic Acid (3b):
Compound **3b** was obtained by the same procedure used for compound **3a** from **4** (8.4 g, 0.062 mol) and 4-methoxyphenol (38.5 g, 0.31 mol); yield: 14.8 g (92%); mp 202 °C (dec).

^{1}H NMR (DMSO-d_6): δ = 3.69 (s, 3H), 5.37 (s, 2H), 6.83 (d, 2H, J = 9.3 Hz), 6.89 (d, 2H, J = 9.3 Hz), 7.50 (dd, 1H, J = 4.8, 7.8 Hz), 8.20 (dd, 1H, J = 1.7, 7.8 Hz), 8.69 (dd, 1H, J = 1.7, 4.8 Hz).

HRMS: *m/z* calc. for $C_{14}H_{13}NO_4$: 259.0845, found 259.0881.

5,11-Dihydro[1]benzoxepino[3,4-*b*]pyridin-5-one (2a):
A mixture of **3a** (37.0 g, 0.16 mol) and PPA (525 g) was stirred at 145 °C for 4 h. The mixture was carefully poured into ice water (7.5 kg), basified with 10 M NaOH (680 mL), and extracted with $CHCl_3$ (3 × 500 mL). The combined $CHCl_3$ extracts were washed with H_2O (500 mL) and concentrated. The residue was recrystallized from EtOAc-hexane (1:2) to afford **2a** as crystals; yield: 21.5 g (64%); mp 60 °C (Lit.[1] mp 58–59 °C from EtOH-H_2O).

^{1}H NMR ($CDCl_3$): δ = 5.33 (s, 2H), 7.02–7.61 (m, 4H), 8.14–8.27 (m, 2H), 8.54 (dd, 1H, J = 1.8, 4.8 Hz).

7-Methoxy-5,11-dihydro[1]benzoxepino[3,4-*b*]pyridin-5-one (2b):
To a solution of **3b** (30.0 g, 0.12 mol) in CH_2Cl_2 (450 mL) was added trifluoroacetic anhydride (61.6 g, 0.29 mol), and the mixture was stirred at r.t. for 1 h, then $BF_3 \cdot OEt_2$ (12.9 g, 0.09 mol) was added. The mixture was refluxed for 5 h and then cooled to r.t. The mixture was poured into ice water (450 mL), then neutralized with 10M NaOH, filtered off and the filtrate was separated. The organic layer was washed with H_2O (150 mL) and concentrated. The residue was recrystallized from EtOH to afford **2b** as crystals; yield: 19.8 g (71%); mp 84°C (Lit.[3] mp 79–80.5°C from *i*-Pr_2O).

^{1}H NMR ($CDCl_3$): δ = 3.86 (s, 3H), 5.32 (s, 2H), 7.07 (d, 1H, J = 8.9 Hz), 7.13 (dd, 1H, J = 3.1, 8.9 Hz), 7.44 (dd, 1H, J = 4.8, 7.9 Hz), 7.66 (d, 1H, J = 3.1 Hz), 8.34 (dd, 1H, J = 1.7, 7.8 Hz), 8.77 (dd, 1H, J = 1.7, 4.8 Hz).

5-{[2-(Diethylamino)ethyl]amino}-5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine (1a); Typical Procedure:
To a suspension of **2a** (21.1 g, 0.10 mol) and *N,N*-diethylethylenediamine (46.5 g, 0.40 mol) in CH_2Cl_2 (200 mL) was added dropwise a solution of $TiCl_4$ (26.6 g, 0.14 mol) in CH_2Cl_2(50 mL) at 10°C, and the mixture was stirred at r.t. for 1 h, The mixture was cooled to 0°C, 2M NaOH (350 mL) was added, and then the mixture was filtered. The filtrate was separated, then the organic layer was washed with H_2O and brine, dried, and concentrated under reduced pressure. To a solution of the residue in HOAc (100 mL) Zn powder (9.2 g, 0.14 mol) was slowly added at 10°C and the mixture was stirred at r.t. for 1 h. The pH of the mixture was adjusted to 12 with 2.5M NaOH and filtered. The filtrate was separated, and extracted with EtOAc (3 × 150 mL). The combined EtOAc extracts were washed with H_2O (150 mL) and brine (150 mL), dried and concentrated under reduced pressure to give the crude **1a** as an oil. The crude free base was dissolved in EtOH (66 mL) and to the solution was added 7 M ethanolic HCl (47.3 mL) at 15°C, and then acetone (340 mL) was added to afford the trihydrochloride of **1a** as crystals; yield: 29.9 g (71%); mp 196°C (dec.) (Lit.[2] mp 195–198°C from *i*-PrOH-acetone).

^{1}H NMR (DMSO-d_6): δ = 1.25 (t, 6H, J = 6.8 Hz), 2.91–3.70 (m, 8H), 5.06 (d, 1H, J = 16.2 Hz), 5.77 (s, 1H), 5.80 (d, 1H, J = 16.2 Hz), 7.15–7.85 (m, 5H), 8.30 (dd, 1H, J = 1.7, 7.6 Hz), 8.67 (dd, 1H, J = 1.7, 5.4 Hz).

5-{[2-(Diethylamino)ethyl]amino}-7-methoxy-5,11-dihydro[1]benzoxepino[3,4-b]pyridine **(1b)**:
The trihydrochloride of compound **1b** was obtained by the same procedure used for the trihydrochloride of compound **1a** from compound **2b** (24.1 g, 0.10 mol) and *N,N*-diethylethylenediamine (46.5 g, 0.40 mol); yield: 37.4 g (83%); mp 188°C (dec.).

^{1}H NMR (DMSO-d_6): δ = 1.23 (t, 6H, J = 7.2 Hz), 2.90–3.75 (m, 8H), 3.77 (s, 3H), 4.94 (d, 1H, J = 16.5 Hz), 5.59 (d, 1H, J = 16.5 Hz), 5.60 (s, 1H), 7.05 (dd, 1H, J = 2.0, 8.8 Hz), 7.20–7.35 (m, 2H), 7.53 (dd, 1H, J = 4.8, 7.8 Hz), 8.30 (dd, 1H, J = 1.5, 7.8 Hz), 8.64 (dd, 1H, J = 1.5, 4.8 Hz).

(1) Tagawa, H.; Kubo, S.; Ishikawa, F. *Chem. Pharm. Bull.* **1981**, *29*, 3515.
(2) Kumazawa, T.; Harakawa, H.; Obase, H.; Oiji, Y.; Tanaka, H.; Shuto, K.; Ishii, A.; Oka, T.; Nakamizo, N. *J. Med. Chem.* **1988**, *31*, 779.
(3) Kumazawa, T.; Harakawa, H.; Obase, H.; Oiji, Y.; Nito, M.; Kudo, K.; Ishii, A.; Tomioka, S.; Yamada, Y. *J. Med. Chem.* **1990**, *33*, 3095.
(4) Kaupmann, A. *Eur. J. Med. Chem.* **1985**, *20*, 207.
(5) Hemmerich, P.; Fallab, S. *Helv. Chim. Acta* **1958**, *61*, 498.
(6) Paul, D.B.; Rodda, H.J. *Aust. J. Chem.* **1969**, *22*, 1759.
(7) Kuhn, R.; Butala, I. *Justus Liebigs Ann. Chem.* **1968**, *718*, 50.
(8) Goto, T.; Konno, M.; Saito, M.; Sato, R. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1205.
(9) Ueno, K.; Kudo, S.; Tagawa, H.; Yoshikawa, T.; Tsukuda, W.; Tsubokawa, M.; Kojima, H.; Kasahara, A. *J. Med. Chem.* **1976**, *19*, 941.