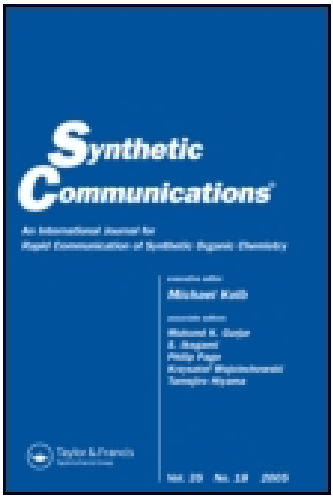

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Facile Synthesis of 1,4-Dihydropyridine Monocarboxylic Acids and Unsymmetric Dicarboxylates via Quaternary Ammonium Salts of 2-Aminoethyl 1,4-Dihydropyridine-3,5-dicarboxylates

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Published online: 22 Aug 2006.

SYNTHETIC COMMUNICATIONS, 27(19), 3321-3331 (1997)

FACILE SYNTHESIS OF 1,4-DIHYDROPYRIDINE MONOCARBOXYLIC ACIDS AND UNSYMMETRIC DICARBOXYLATES *VIA* QUATERNARY AMMONIUM SALTS OF 2-AMINOETHYL 1,4-DIHYDROPYRIDINE-3,5-DICARBOXYLATES

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ABSTRACT: Useful 1,4-dihydropyridine unsymmetric dicarboxylates [nitrendipine (**1**), nicardipine (**2**)] and monocarboxylic acid **4** were prepared from unsymmetric 2-aminoethyl methyl 1,4-dihydropyridine-3,5-dicarboxylates **2** and **3** *via* their corresponding quaternary ammonium salts **5-9**.

1,4-Dihydropyridine-3,5-dicarboxylate derivatives have gained much interest as potent calcium channel blockers.[1-3] Unsymmetric 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylates such as nitrendipine (**1**)[4] and nicardipine (**2**)[5] are widely used for the treatment of angina pectoris and hypertension (**FIG. 1**). 3-(1-Benzyl-3-piperidyl) methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3**) has an especially mild,

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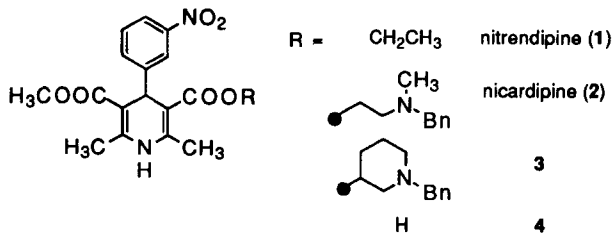


FIG. 1

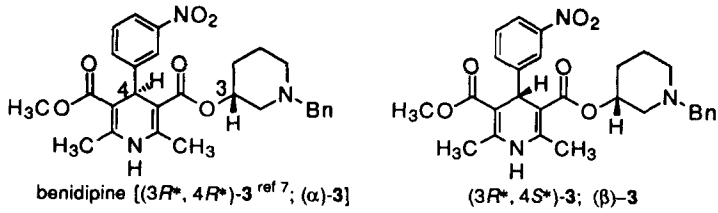
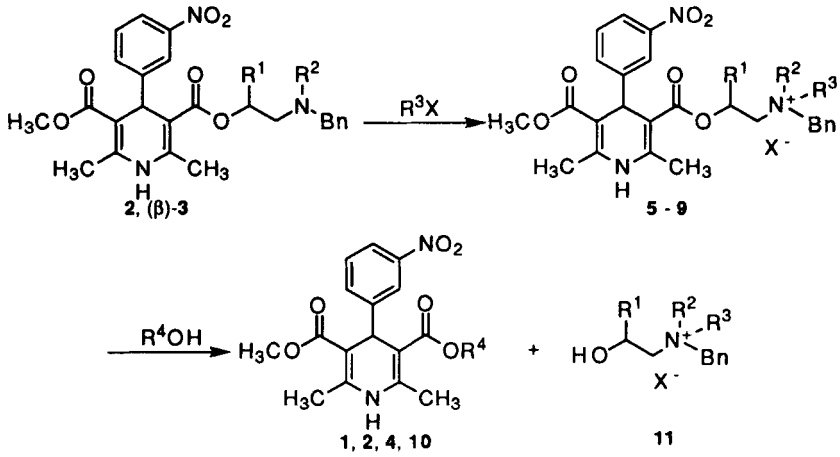


FIG. 2

highly potent and long-lasting antihypertensive effect.[6] This compound **3** possesses two asymmetric carbons; C-4 of the dihydropyridine ring and C-3 of piperidine (**FIG. 2**). As for compound **3**, the racemic (3*R**, 4*R**)-isomer,[7] named α-isomer; (α)-**3**,[6,8] showed very strong antihypertensive effect, but little activity was observed in the (3*R**, 4*S**)-isomer; (β)-**3**. The racemic compound (α)-**3** named benidipine[9] is synthesized by the Hantzsch reaction[10,11] similar to the synthesis of the common dihydropyridine compounds, therefore, it is impossible to control the diastereoisomer ratio of (α)-**3** and (β)-**3** by the reaction conditions. The method for the separation of (α)-**3** from the mixture of the diastereoisomers in industrial production has been completely achieved,[11] however, it is worth reclaiming (β)-**3** for reducing production costs and environmental concerns. From the view point of reclamation of (β)-**3**, we started



Scheme

researching the effective transformation of (β)-**3** to valuable compounds. It is well-known that some types of 2-substituted ethyl esters are used for protecting the carboxyl group. In the synthesis of some dihydropyridines, the selective cleavage of the 2-cyanoethyl ester group, for example, lead to 1,4-dihydropyridine monocarboxylic acid **4**,[12-14] which is a useful intermediate for the synthesis of unsymmetric 1,4-dihydropyridine-3,5-dicarboxylate derivatives. If the aminoethyl moiety in the *N*-benzylpiperidinyl ester of (β)-**3** is able to be converted into activated intermediates mentioned above, some useful compounds such as **1**, **2** or **4** would be easily and cheaply supplied from them. We then planned to activate the aminoethyl moiety of (β)-**3** by exhaustive alkylation of the tertiary nitrogen atom with alkyl halides and attempt selective hydrolysis and alcoholysis (**Scheme**).[15] Herein, we report our attempts and results for developing a new method of deprotection in the dihydropyridinedicarboxylate chemistry using quaternary ammonium salts.

The quaternary ammonium salts **5-9** were easily obtained as precipitates from the reaction mixture by exhaustive alkylation of **2** and (β)-**3** with their corresponding alkyl halides, such as methyl iodide, benzyl bromide or allyl bromide in high yields, respectively (**Scheme**, **Table 1**). The alkylation at the nitrogen atom of the 1,4-dihydropyridine ring was not observed under these reaction conditions, since the nucleophilicity of the nitrogen might be decreased due to the enamine resonance. Therefore, the protection of the nitrogen atom of the dihydropyridine ring was not necessary in these reactions. The existence of the diastereoisomers for compounds **5**, **7** and **9** were observed by ^{1}H NMR analysis, however, the diastereoisomers could not be separated by several analytical methods such as TLC and HPLC analyses.

Table 1. Synthesis of Quaternary Ammonium Salts **5-9** [a]

Substrate	R^1	R^2	R^3X	(equiv[b])	Solvent	Product	Yield (%)[c]
(β)-**3**	-$(CH_2)_3$-		MeI	(1.2)	acetone	**5**	94
(β)-**3**	-$(CH_2)_3$-		BnBr	(2.0)	$CHCl_3$	**6**	93
(β)-**3**	-$(CH_2)_3$-		H_2C=$CHCH_2Br$	(1.1)	$CHCl_3$	**7**	95
2	H	Me	MeI	(1.2)	acetone	**8**	93
2	H	Me	H_2C=$CHCH_2Br$	(1.1)	$CHCl_3$	**9**	99

[a] All reactions were carried out at reflux temperature. [b] Based on the substrate. [c] Isolated yield based on the substrate.

For the alkaline hydrolysis of the quaternary ammonium salt, an aqueous sodium hydroxide was selected as the base. Compound **6** was smoothly hydrolyzed with 1 M sodium hydroxide in THF at 40 °C. After being quenched by the addition of hydrochloric acid, the corresponding 5-methoxycarbonyl-1,4-dihydropyridine-3-carboxylic acid **4**[12,13] was obtained as a white precipitate (68% yield, **Scheme**, **Table 2**). The compound **3** [(α)-**3** and (β)-**3**], by contrast with compound **6** which bears the activated ester moiety, resisted to hydrolysis even under severe conditions such as high concentration of base in THF and elevated

temperature. Compounds **5**, **7** and **9** similarly gave **4** in moderate yields (69 - 72% yield, **Table 2**).

Table 2. Synthesis of **4** by Hydrolysis of Quaternary Ammonium Salts [a]

Substrate	R^1 R^2	R^3	X	Yield of **4** (%) [b]
5	$-(CH_2)_3-$	Me	I	71
6	$-(CH_2)_3-$	Bn	Br	68
7	$-(CH_2)_3-$	$H_2C=CHCH_2-$	Br	69
9	H Me	$H_2C=CHCH_2-$	Br	72

[a] All reactions were carried out at 40 °C with 1 M NaOH (3.0 equiv based on the substrate).
[b] Isolated yield based on the substrate.

Next, the alkaline alcoholysis of the quaternary ammonium salts was investigated in order to obtain compounds **1** and **2** directly from the salts. The reactions were carried out in ethanol with 1.1 equiv of potassium hydroxide to give nitrendipine (**1**) from the salts **5-8** in high yields (85 - 92% yield, **Table 3**).

Table 3. Synthesis of **1** by Ethanolysis of Quaternary Ammonium Salts [a]

Substrate	R^1 R^2	R^3	X	Yield of **1** (%) [b]
5	$-(CH_2)_3-$	Me	I	91
6	$-(CH_2)_3-$	Bn	Br	92
7	$-(CH_2)_3-$	$H_2C=CHCH_2-$	Br	85
8	H Me	Me	I	92

[a] All reactions were carried out in ethanol with KOH (1.1 equiv based on the substrate) at 25 °C.
[b] Isolated yield based on the substrate.

In order to confirm the reaction pathway, we investigated the formation of the expected quaternary ammonium salt **11**. When compound **8** was exposed in methanol-*d4* with 1.2 equiv of sodium deuteroxide at 25 °C in an NMR tube, benzyl (2-hydroxyethyl)dimethylammonium iodide (**11**; R^1=H, R^2=R^3=CH_3, X=I)[16] was proved by ^{1}H NMR analysis to be quantitatively obtained along with methyl methyl-*d3* 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**10**; R^4=CD_3). From this evidence, the alkaline alcoholysis of the

quaternary ammonium salts could occur as described in the scheme. The driving force of this selective cleavage might be an inductive effect by the electron-withdrawing quaternary ammonium group. In the case of the synthesis of nicardipine (**2**), the reactions were carried out with 1.2 equiv of 2-(*N*-benzyl-*N*-methylamino)ethanol using 1.1 equiv of a base such as sodium hydride, potassium hydroxide and sodium hydroxide in THF at 25 °C. The yields of **2** had a large difference depending on the starting quaternary ammonium salts **5-7** (16 - 67% yield, **Table 4**). Much remains to be learned about the reactivities of the salts **5-7** during alkaline alcoholysis. In the case of using the secondary alcohols such as 1-benzyl-3-hydroxypiperidine (side chain of **3**) or *i*-propanol, however, these reactions did not proceed even at higher temperatures. The steric hindrance between the secondary alcohols used and the quaternary ammonium salts of the 1,4-dihydropyridine would lower the reactivities.

Table 4. Synthesis of **2** by Alcoholysis of Quaternary Ammonium Salts [a]

Substrate	R^1 R^2	R^3	X	Base [b]	Yield of **2** (%) [c]
5	$-(CH_2)_3-$	Me	I	KOH	32
6	$-(CH_2)_3-$	Bn	Br	NaH	53
6	$-(CH_2)_3-$	Bn	Br	NaOH	62
6	$-(CH_2)_3-$	Bn	Br	KOH	67
7	$-(CH_2)_3-$	$H_2C{=}CHCH_2-$	Br	NaH	18
7	$-(CH_2)_3-$	$H_2C{=}CHCH_2-$	Br	NaOH	16
7	$-(CH_2)_3-$	$H_2C{=}CHCH_2-$	Br	KOH	26

[a] All reactions were carried out with 2-(*N*-benzyl-*N*-methylamino)ethanol (1.2 equiv based on the substrate) in THF at 25 °C. [b] 1.1 equiv based on the substrate. [c] Isolated yield based on the substrate.

In conclusion, several unsymmetric 2-aminoethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylates are converted into useful compounds, such as unsymmetric dicarboxylates [nitrendipine (**1**), nicardipine (**2**)]

and monocarboxylic acid **4**, *via* their corresponding quaternary ammonium salts. This methodology would supply a reclamation of the useless (β)-**3** and a new deprotection in the dihydropyridinedicarboxylate chemistry.

Experimental Section

Melting points were determined using a Mettler FP62 melting point instrument and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AC300 spectrometer and signals are given in ppm using TMS as an internal standard. IR spectra were recorded on a Shimadzu FTIR-4300 spectrophotometer. MS spectra were recorded on a JEOL JMS-D300 spectrometer. Elemental analyses were performed using a Yanaco MT-3 CHN corder. All reagents and solvents were of commercial quality.

Compounds **2**[5] and (β)-**3**[6,11] were prepared according to the reported procedures.

(3*R)-1-Benzyl-1-methyl-3-[(4*S**)-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carbonyl]oxy-piperidinium iodide (5): Typical Procedure of Quaternary Ammonium Salt.** To a solution of (3*R**)-1-benzyl-3-piperidyl methyl 1,4-dihydro-2,6-dimethyl-(4*S**)-(3-nitrophenyl)-3,5-pyridinedicarboxylate [(β)-**3**, 5.05 g, 10.0 mmol] in acetone (25 mL) was dropwise added methyl iodide (0.93 mL, 12.0 mmol), and the mixture was refluxed for 8 h. After cooling, the mixture was concentrated to dryness under reduced pressure. To the resulting residue was added toluene (40 mL) and the mixture was stirred for 10 min. The precipitated crystals were filtered, washed with toluene, and dried under vacuum to afford **5** as a yellow amorphous solid; 6.10 g (94%); mp 128 - 129 °C (dec.); ^{1}H NMR (DMSO-*d*$_6$/TMS): δ = 1.5 - 2.2 (m, 4H), 2.26 (s, 3H), 2.33 (s, 3H), 2.73 (s, 3H × 1/3), 2.94 (s, 3H × 2/3), 3.1 - 3.5 (m, 4H), 3.49 (s, 3H × 2/3), 3.51 (s, 3H × 1/3), 4.35 - 4.65 (m, 2H), 4.91 (s, 1H × 2/3), 4.94 (s, 1H × 1/3), 5.16 (br s, 1H × 2/3), 5.30 (br s, 1H × 1/3), 7.3 - 7.6 (m, 7H), 7.88 (t, *J* = 1.9 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 9.24 (s, 1H); IR (KBr): υ = 1695, 1530, 1350, 1215 cm^{-1}; HRMS: calcd for $C_{29}H_{34}N_3O_6$ *m/z* 520.2448 (M^+-I), found 520.2449.

(3*R)-1,1-Dibenzyl-3-[(4*S**)-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carbonyl]oxy-piperidinium bromide (6).** mp 188 - 190 °C (dec.); ^{1}H NMR (DMSO-

d6/TMS): δ = 1.4 - 2.2 (m, 4H), 2.29 (s, 3H), 2.36 (s, 3H), 2.6 - 3.4 (m, 4H), 3.44 (s, 3H), 4.49 (d, *J* = 12.2 Hz, 1H), 4.62 (d, *J* = 12.2 Hz, 1H), 4.81 (s, 2H), 4.96 (s, 1H), 5.44 (br s, 1H), 7.3 - 7.6 (m, 12H), 7.88 (t, *J* = 1.9 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 9.24 (s, 1H); IR (KBr): υ = 1695, 1530, 1350, 1210 cm^{-1}; HRMS: calcd for $C_{35}H_{38}N_3O_6$ *m/z* 596.2761 (M^+-Br), found 596.2770.

(3*R)-1-Allyl-1-benzyl-3-[(4*S**)-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carbonyl]oxypiperidinium bromide (7).** mp 156 - 157 °C (dec.); ^1H NMR (DMSO-*d6*/TMS): δ = 1.5 - 2.2 (m, 4H), 2.29 (s, 3H × 2/3), 2.34 (s, 3H × 2/3), 2.31 (s, 3H × 1/3), 2.36 (s, 3H × 1/3), 2.8 - 3.4 (m, 4H), 3.33 (s, 3H × 2/3), 3.35 (s, 3H × 1/3), 3.6 - 3.8 (m, 2H × 1/3), 3.9 - 4.1 (m, 2H × 2/3), 4.49 (m, 2H × 2/3), 4.62 (m, 2H × 1/3), 4.91 (s, 1H × 2/3), 4.93 (s, 1H × 1/3), 5.15 - 5.3 (m, 1H × 2/3), 5.3 - 5.4 (m, 1H × 1/3), 5.49 (d, *J* = 15.7 Hz, 1H × 1/3), 5.60 (d, *J* = 11.5 Hz, 1H × 1/3), 5.69 (d, *J* = 11.5 Hz, 1H × 2/3), 5.78 (d, *J* = 15.7 Hz, 1H × 2/3), 6.0 - 6.1 (m, 1H × 1/3), 6.1 - 6.2 (m, 1H × 2/3), 7.3 -7.6 (m, 7H), 7.91 (t, *J* = 1.9 Hz, 1H × 2/3), 7.93 (t, *J* = 1.9 Hz, 1H × 1/3), 8.0 - 8.1 (m, 1H), 9.04 (s, 1H); IR (KBr): υ = 1705, 1530, 1350, 1210 cm^{-1}; HRMS: calcd for $C_{31}H_{36}N_3O_6$ *m/z* 546.2604 (M^+-Br), found 546.2613.

Benzyl-dimethyl-[5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carbonyl]oxyethanoammonium iodide (8). mp 172 - 173 °C (dec.); ^1H NMR (DMSO-*d6*/TMS): δ = 2.25 (s, 3H), 2.35 (s, 3H), 2.90 (s, 6H), 3.33 (s, 3H), 3.51 (br s, 2H), 4.4 - 4.6 (m, 4H), 4.99 (s, 1H), 7.2 - 7.6 (m, 7H), 7.9 (m, 2H), 9.22 (s, 1H); IR (KBr): υ = 1690, 1660, 1530, 1350, 1215 cm^{-1}; HRMS: calcd. for $C_{27}H_{32}N_3O_6$ *m/z* 494.2291 (M^+-I), found 494.2283; Anal: calcd for $C_{27}H_{32}IN_3O_6$: C, 52.18; H, 5.19; N, 6.76, found: C, 52.25; H, 5.28; N, 6.52.

Allyl-benzyl-methyl-[5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carbonyl]oxypiperidinium bromide (9). mp 104 - 110 °C (dec.); ^1H NMR (DMSO-*d6*/TMS): δ = 2.25 (s, 3H), 2.36 (s, 3H), 2.85 (s, 3H × 1/2), 2.85 (s, 3H × 1/2), 3.4 - 3.6 (m, 2H), 3.54 (s, 3H × 1/2), 3.55 (s, 3H × 1/2), 3.75 - 3.9 (m, 1H), 4.0 - 4.15 (m, 1H), 4.4 - 4.55 (m, 4H), 4.97 (s, 1H × 1/2), 4.98 (s, 1H × 1/2), 5.6 - 5.7 (m, 2H), 6.0 - 6.1 (m, 1H), 7.1 - 7.6 (m, 7H), 7.9 (m, 2H), 9.27 (s, 1H); IR (KBr): υ = 1690, 1530, 1350, 1212 cm^{-1}; HRMS: calcd for $C_{29}H_{34}N_3O_6$ *m/z* 520.2448 (M^+-Br), found 520.2449.

5-Methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid (4): Typical Procedure. To a suspension of **6** (6.77 g, 10 mmol) in THF (30 mL) was dropwise added 1 M NaOH (30 mL), and the mixture was stirred for 5 h at 40 °C. After cooling, the reaction mixture was concentrated under reduced pressure. EtOAc (20 mL) was added to the concentrate, the organic layer was separated and its pH was adjusted to 2.5 by adding 4 M HCl. Then, the precipitated crystals were filtered, washed with EtOAc, and dried under vacuum to afford **4**[12,13] as a white crystal; 2.26 g (68%); mp 192 - 193 °C (dec.); ^{1}H NMR (DMSO-*d*$_6$/TMS): δ = 2.28 (s, 3H), 2.29 (s, 3H), 3.55 (s, 3H), 5.00 (s, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.59 (m, 1H), 7.95 - 8.00 (m, 2H), 8.96 (s, 1H), 11.8 (br s, 1H).

Ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1): Typical Procedure. KOH (73 mg, 1.1 mmol) was added to EtOH (2.0 mL), and the mixture was stirred for 30 min at 25 °C. To the alkaline EtOH was added **6** (677 mg, 1.0 mmol), and the mixture was stirred for 24 h at 25 °C. Toluene (10 mL) was added to the reaction mixture, and washed with H_2O (10 mL). The organic layer was separated and concentrated under reduced pressure to dryness. The resulting residue was purified by column chromatography (silica gel, 2:1 *n*-hexane/EtOAc as an eluent) followed by drying under vacuum to afford **1**[14] as a yellow solid; 330 mg (92%); ^{1}H NMR ($CDCl_3$/TMS): δ = 1.23 (t, *J* = 7.2 Hz, 3H), 2.37 (s, 3H), 2.38 (s, 3H), 3.64 (s, 3H), 4.09 (q, *J* = 7.2 Hz, 2H), 5.10 (s, 1H), 5.69 (s, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.63 (dt, *J* = 7.9, 1.4 Hz, 1H), 8.00 (ddd, *J* = 7.9, 2.2, 1.1 Hz, 1H), 8.11 (t, *J* = 2.0 Hz, 1H).

2-(*N*-Benzyl-*N*-methylamino)ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2): Typical Procedure. To the mixture of 2-(*N*-benzyl-*N*-methylamino)ethanol (1.98 g, 1.2 mmol) and THF (5.0 mL) was added KOH (73 mg, 1.1 mmol), and the mixture was stirred for 30 min at 25 °C. To the alkaline solution was added **6** (677 mg, 1.0 mmol), and the mixture was stirred for 24 h at 25 °C. Toluene (5 mL) was added to the reaction mixture, and washed three times with H_2O (2 mL). The organic layer was separated and concentrated under reduced pressure to dryness. The resulting residue was purified by column chromatography (silica gel, 20:1 $CHCl_3$/MeOH as an eluent) followed by drying under vacuum to afford **2**[5] as a yellow solid; 319 mg (67%); ^{1}H NMR ($CDCl_3$/TMS): δ = 2.20 (s, 3H), 2.35 (s, 3H), 2.37 (s, 3H),

2.61 (dt, J = 13.1, 6.0 Hz, 1H), 2.66 (dt, J = 13.1, 6.0 Hz, 1H), 3.50 (s, 2H), 3.64 (s, 3H), 4.17 (t, J = 6.0 Hz, 2H), 5.13 (s, 1H), 5.84 (s, 1H), 7.2 - 7.3 (m, 5H), 7.32 (t, J = 8.1 Hz, 1H), 7.65 (dt, J = 7.7, 1.3 Hz, 1H), 7.97 (ddd, J = 8.1, 2.4, 1.1 Hz, 1H), 8.10 (t, J = 2.2 Hz, 1H).

Acknowledgment. We thank Dr. Masaji Kasai for useful discussions regarding this work.

References and Notes

1. Vater, W., Kroneberg, G., Hoffmeuster, H., Kaller, H., Meng, K., Oberdorf, A., Plus, W., Schloßmann, K. and Stoepel, K. *Arzneim.-Forsch.*, **1972**, *22*, 1.
2. Fleckenstein, A., Tritthart, H.J., Döring, H.J. and Byon, K.Y. *Arzneim.-Forsch.*, **1972**, *22*, 22.
3. Fleckenstein, A. and Grün, G. *Arzneim.-Forsch.*, **1972**, *22*, 334.
4. Meyer, H., Bossert, F., Wehinger, E., Stoepel, K. and Vater, W. *Arzneim.-Forsch.*, **1981**, *31*, 407.
5. Iwanami, M., Shibanuma, T., Fujimoto, M., Kawai, R., Tamazawa, K., Takenaka, T., Takahashi, K. and Murakami, M. *Chem. Pharm. Bull.*, **1979**, *27*, 1426.
6. Muto, K., Kuroda, H., Kawato, H., Karasawa, A., Kubo, K. and Nakamizo, N. *Arzneim.-Forsch.*, **1988**, *38*, 1662.
7. The symbols in parentheses indicate the configuration of piperidine C-3 position and dihydropyridine C-4 position, respectively.
8. Compound **3** gave two spots on TLC[17] (50:50:1 CH_2Cl_2/EtOAc/Et_3N as a developing solvent). The isomer giving a higher R_f spot under this condition was (3*R**, 4*R**)-isomer and named α-isomer.[6] Moreover, it was also reported that the α-isomer preferentially crystallized with good selectivity by fractional crystallization of the hydrochloride of **3**.[6]
9. The racemic compound (α)-**3** was named benidipine, and its hydrochloride have been manufactured as Coniel® by Kyowa Hakko Kogyo Co., Ltd.
10. Hantzsch, A. *Liebigs Ann. Chem.*, **1882**, *215*, 1.
11. Details of synthetic study of benidipine hydrochloride will be published elsewhere by T. Ogasa *et al.*

12. Wehinger, E. and Bossert, F. Ger. Patent 2847237, 1980; *Chem. Abstr.* **1980**, *93*, 150124.
13. Ogawa, T., Hatayama, K., Maeda, H. and Kita, Y. *Chem. Pharm. Bull.*, **1994**, *42*, 1579.
14. The practical syntheses of the chiral 1,4-dihydropyridine monocarboxylic acid **4** by lipase-catalyzed enantioselective hydrolysis, as the key reactions, were reported in the following literatures: Ebiike, H., Terao, Y. and Achiwa, K. *Tetrahedron Lett.*, **1991**, *32*, 5805. Hirose, Y., Kariya, K., Sasaki, I., Kurono, Y., Ebiike, H. and Achiwa, K., *Tetrahedron Lett.*, **1992**, *33*, 7157.
15. 2-Benzoyloxyethyltrimethylammonium iodide was sensitive to alkaline to yield benzoic acid and 2-hydroxyethyltrimethylammonium iodide, was investigated by Mamalis and Rydon, as one example of the alkaline cleavage of 2-substituted ethyl ester in the following literature. To our knowledge, the alkaline cleavage of such quaternary ammonium salts has not been mentioned except the example: Mamalis, P. and Rydon, H.N. *J. Chem. Soc.*, **1955**, 1049.
16. Compound **11** (R^1=H, R^2=R^3=CH_3, X=I) was prepared by a similar manner described in experimental section.
17. Silica gel plate is Merck Art 11798 from Merck Co., Ltd. in Germany.

(Received in Japan 3 February 1997)