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Synthesis of the Metabolites of 2-(N-Benzyl-N-methylamino)ethyl Methyl 2,6-Dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate Hydrochloride (Nicardipine Hydrochloride,[1] YC-93)

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Eight metabolites (M-1—M-6, M-8, M-9) of 2-(N-benzyl-N-methylamino)ethyl methyl 2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate hydrochloride (YC-93) were synthesized and the structures of the metabolites were established by comparison with the synthetic compounds.

Keywords——metabolites; dihydropyridine; pyridine; catalytic hydrogenation; lactone; selective hydrolysis; oxidation; Hantzsch method; vasodilator

In a previous paper,[3] 2-(N-benzyl-N-methylamino)ethyl methyl 2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate hydrochloride (YC-93) was shown to be a powerful vasodilator among various water-soluble dihydropyridine derivatives tested. The metabolic fate of this compound has been investigated by Higuchi and co-workers.[4] As a result of their studies, eight metabolites (M-1—M-6, M-8, M-9)[5] were isolated from the urine of the dogs and rats administered YC-93 and their structures were elucidated.

In order to confirm the structures of these metabolites and to clarify their pharmacological properties, methods of the synthesis of these metabolites have been studied.[6] This paper describes the syntheses of these metabolites.

Synthesis of (M-1)

(M-1) was prepared by the route shown in Chart 1. Treatment of 2-(N-methylamino)-ethanol (**1**) with ethyl formate afforded 2-(N-formyl-N-methylamino)ethanol (**2**), which was allowed to react with diketene to give 2-(N-formyl-N-methylamino)ethyl acetoacetate (**3**). The 1,4-dihydropyridine (**4**) which was obtained by the condensation of **3**, methyl 3-aminocrotonate and *m*-nitrobenzaldehyde, was hydrolyzed with *p*-toluenesulfonic acid in EtOH–MeOH (1: 1) to give methyl 2-(N-methylamino)ethyl 2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**5**) in 17.8% overall yield from **1**.

The compound (**5**) thus synthesized was identical with the metabolite (M-1), judging from their nuclear magnetic resonance (NMR) and mass (MS) spectra and behaviour on thin-layer chromatography (TLC).[4]

Synthesis of (M-2—M-5)

(M-2—M-5) were synthesized by the route illustrated in Chart 2. 2-(N-Benzyl-N-methyl-amino)ethyl methyl 4-(*m*-aminophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

1) Prop. INN: WHO Chronicle, 33, Supplement (List 42), 13 Sept., 1979, The code designation of the hydrochloride of nicardipine is YC-93.
2) Location: *Azusawa 1-1-8, Itabashi-ku, Tokyo 174, Japan.*
3) M. Iwanami, T. Shibanuma, M. Fujimoto, R. Kawai, K. Tamazawa, T. Takenaka, K. Takahashi, and M. Murakami, *Chem. Pharm. Bull.*, **27**, 1426 (1979).
4) S. Higuchi, H. Sasaki, Y. Shiobara, and T. Sado, *Xenobiotica*, **7**, 469 (1977).
5) In a previous paper, the eight metabolites were designated as (M-1—M-6), (M-8) and (M-9).
6) M. Iwanami and M. Murakami, Jpn. Patent (Kokai) 131970 (1975).

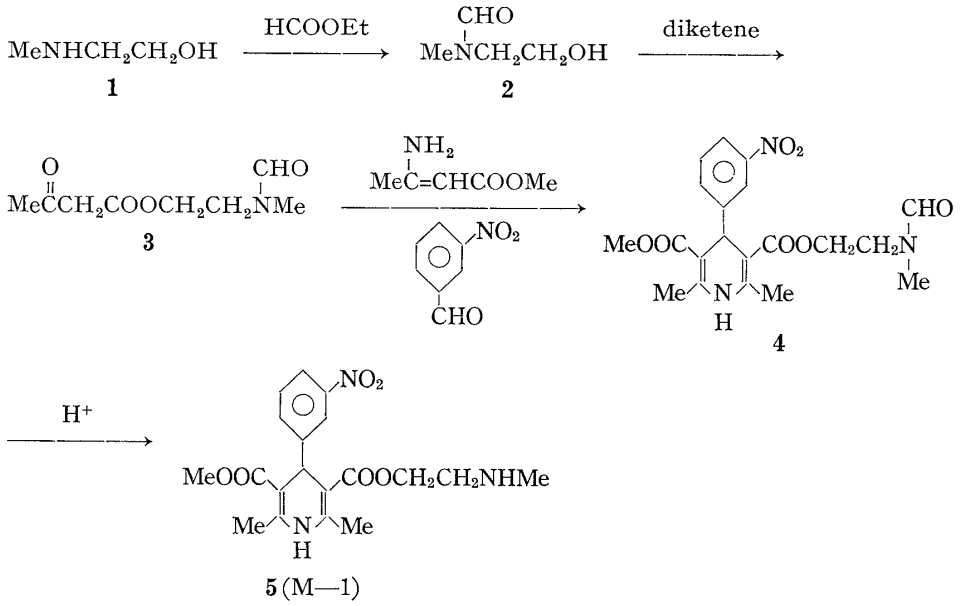

Chart 1

(**7**) was prepared by selective reduction of the nitro group of **6** with hydrogen and Raney nickel without affecting the N-benzyl group.[3] Further, **7** was debenzylated by catalytic hydrogenation with 10% Pd–C to afford methyl 2-(N-methylamino)ethyl 4-(*m*-aminophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**8**).

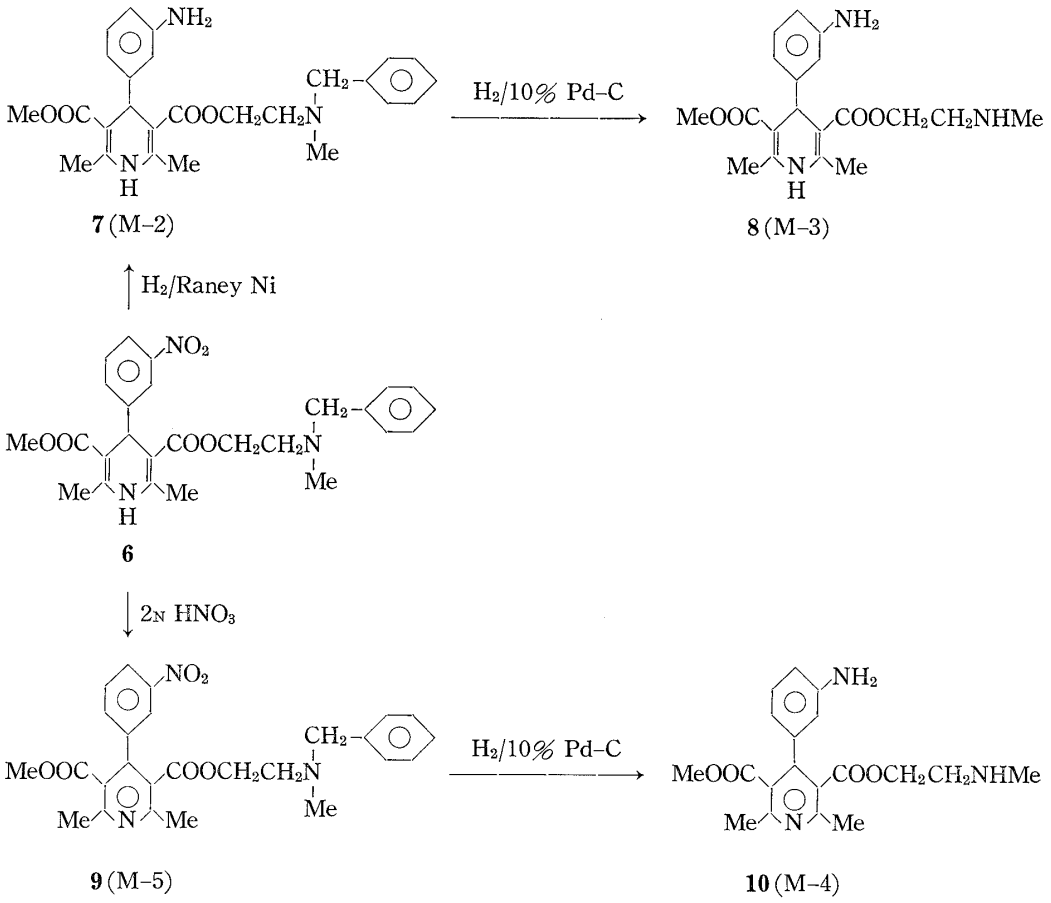

Chart 2

2-(N-Benzyl-N-methylamino)ethyl methyl 2,6-dimethyl-4-(*m*-nitrophenyl)pyridine-3,5-dicarboxylate (**9**) was obtained by the oxidation of **6** with 2 N nitric acid using a method similar to that described by Cook *et al.*[7] Subsequently, **9** was hydrogenated over 10% Pd–C to give methyl 2-(N-methylamino)ethyl 4-(*m*-aminophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (**10**).

The compounds (**7**, **8**, **9** and **10**) were identical with the metabolites (M-2), (M-3), (M-5) and (M-4), respectively, as judged by direct comparison (NMR and MS spectra and *Rf* values on TLC).[4]

Synthesis of (M-6), (M-8) and (M-9)

The synthetic routes to (M-6), (M-8) and (M-9) are shown in Chart 3. Dimethyl 2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**11**), which was obtained by the Hantzsch method,[8] was oxidized with 2N nitric acid to the corresponding pyridine[7] (**12**). Hydrolysis of **12** with 1 eq. of KOH afforded 5-methoxycarbonyl-2,6-dimethyl-4-(*m*-nitrophenyl)pyridine-3-carboxylic acid (**13**). Further, heating of **13** with 40% peracetic acid in EtOH gave the N-oxide (**14**). The N-oxide (**14**) was converted on treatment with acetic anhydride to the acetate (**15**), which, without further purification, was hydrolyzed with KOH in MeOH, followed by heating with 6 N HCl to produce 3-methoxycarbonyl-2-methyl-4-(*m*-nitrophenyl)-5-oxo-5,7-dihydrofuro[3,4-*b*]pyridine[9] (**16**).

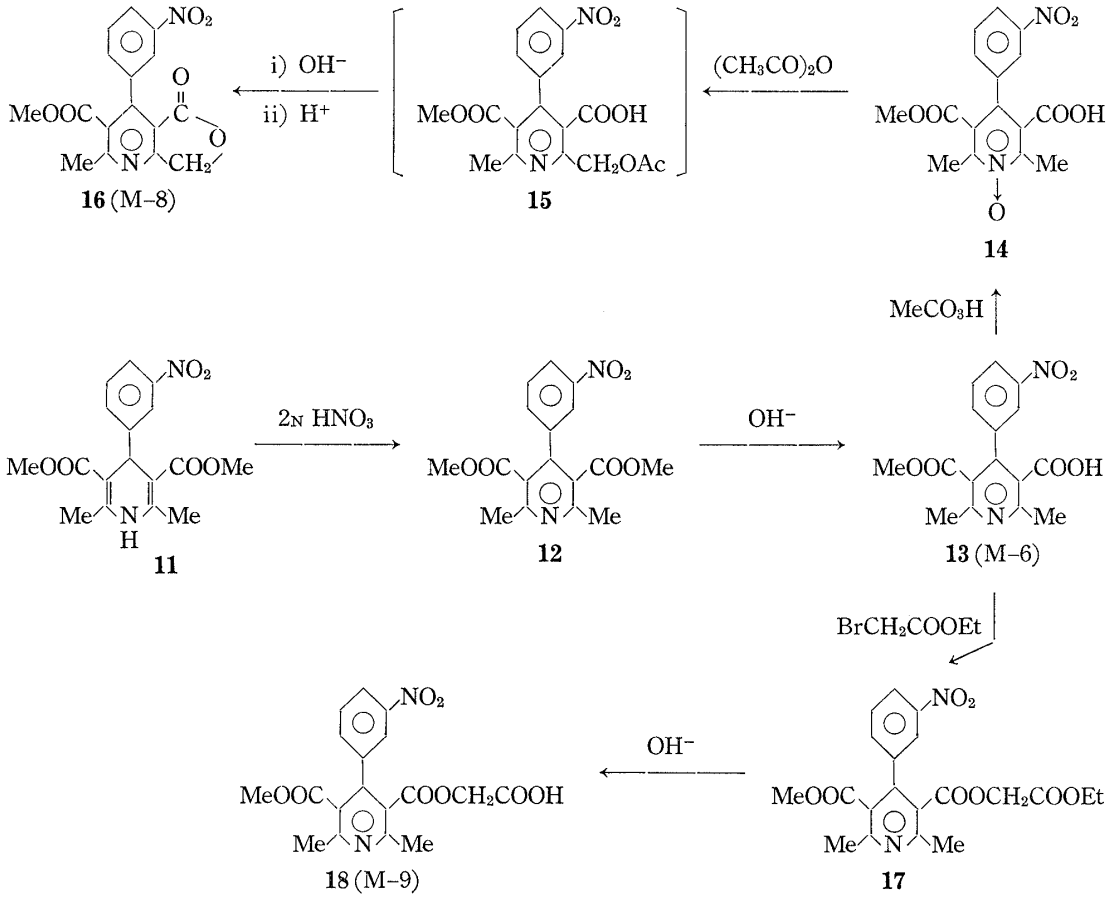

Chart 3

7) A.H. Cook, I.M. Heilbron, and L. Steger, *J. Chem. Soc.*, **1943**, 413.
8) A. Hantzsch, *Ann. Chim.*, **215**, 1 (1882).
9) *a*) S. Oae, T. Kitao, and Y. Kitaoka, *J. Am. Chem. Soc.*, **84**, 3359 (1962); *b*) S.E. Parker and J. Weinstock, *J. Med. Chem.*, **16**, 34 (1973).

On the other hand, the sodium salt of **13** was treated with ethyl bromoacetate to give the ester (**17**). The ethyl ester group of **17** was exclusively hydrolyzed with 1 eq of KOH in MeOH to yield carboxymethyl methyl 2,6-dimethyl-4-(*m*-nitrophenyl) pyridine-3,5-dicarboxylate (**18**).

The *Rf* values on TLC and major peaks in the NMR and MS spectra of M-6, M-8 and M-9 coincided well with those of the synthetic products (**13**, **16** and **18**), respectively.[4] In addition, (M-1—M-5) each had vasodilating activity, although the activity was less than 1/100 of that of YC-93; (M-6), (M-8) and (M-9) were inactive.

Experimental

All melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded with a JEOL MH-100 spectrometer (100 MHz) using Me_4Si as an internal standard. The following abbreviations are used; s=singlet, d=doublet, t=triplet, m=multiplet. Mass spectra (MS) were measured on a Hitachi RMU-6MG spectrometer. Infrared spectra (IR) were taken with a Hitachi 215 grating spectrophotometer. All evaporation procedures were carried out *in vacuo*.

2-(N-Formyl-N-methylamino)ethanol (2)——A mixture of 2-(N-methylamino)ethanol (34 g) and ethyl formate (50 g) was refluxed for 1 hr. The reaction mixture was concentrated to afford **2** (36 g), which was used for the next reaction without further purification. (bp 130—132° (0.2—0.4 Torr)) NMR ($CDCl_3$) δ: 2.86, 3.00 (3H, s, $-\overset{|}{N}-CH_3$), 3.35 (2H, t, $-CH_2\overset{|}{N}-$), 3.67 (2H, t, $-CH_2O-$), 8.00 (1H, s, -CHO).

2-(N-Formyl-N-methylamino)ethyl Acetoacetate (3)——Diketene (17 g) was added dropwise with stirring to **2** (21 g) at 80—85°. When the addition was complete, the temperature was maintained at 80—85° for 1 hr. The acetoacetate (**3**) formed was used without distillation. NMR ($CDCl_3$) δ: 2.28 (3H, s, CH_3CO-), 2.80, 3.01 (3H, s, $-\overset{|}{N}-CH_3$), 3.50 (2H, s, $-COCH_2COO-$), 3.60 (2H, t, $-CH_2C\underline{H}_2\overset{|}{N}-$), 4.30 (2H, t, $-COOC\underline{H}_2CH_2-$).

2-(N-Formyl-N-methylamino)ethyl Methyl 2,6-Dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4)——A mixture of the acetoacetate (**3**) (22 g), methyl 3-aminocrotonate (13.6 g) and *m*-nitrobenzaldehyde (18 g) in iso-PrOH (66 ml) was heated under reflux for 10 hr. After removal of the solvent, the residue was cooled in an ice bath, and then the resulting precipitate was collected and washed with cold iso-PrOH to give the dihydropyridine (**4**) (15 g). NMR ($CDCl_3$) δ: 2.32 (3H, s, $C_{2,6}-CH_3$), 2.84, 2.89 (3H, s, $-\overset{|}{N}-CH_3$), 3.50 (2H, t, $-CH_2C\underline{H}_2\overset{|}{N}-$), 3.64 (3H, s, $-COOCH_3$), 4.21 (2H, t, $-COOC\underline{H}_2CH_2-$), 5.40 (1H, s, C_4-H), 7.38—7.92 (4H, m, C_4-aromatic protons), 8.12 (1H, s, -CHO).

2-(N-Methylamino)ethyl Methyl 2,6-Dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (5) (M-1)——A mixture of the dihydropyridine (**4**) (2.0 g) and *p*-toluenesulfonic acid (0.9 g) in MeOH–EtOH (1: 1) (10 ml) was refluxed for 7 hr. After addition of H_2O (20 ml), the solution was neutralized with $NaHCO_3$ and extracted with AcOEt. The extract was dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (4: 1). The eluate was concentrated to yield **5** (0.8 g). Its hydrochloride was obtained by treatment with EtOH–HCl. mp 138—140°. NMR (base) (d_6-DMSO) δ: 2.24 (6H, s, $C_{2,6}-CH_3$), 2.40 (3H, s, $-NHC\underline{H}_3$), 2.92 (2H, t, $-CH_2C\underline{H}_2NH-$), 3.52 (3H, s, $-COOCH_3$), 4.20 (2H, t, $-COOC\underline{H}_2CH_2-$), 5.00 (1H, s, C_4-H), 7.1—7.6 (4H, m, C_4-aromatic protons), 9.12 (1H, s, dihydropyridine ring $-\overset{|}{N}H$). MS *m/e*: 389 (M^+).

2-(N-Benzyl-N-methylamino)ethyl Methyl 4-(*m*-Aminophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7) (M-2)——**6** (15 g) in THF (10 ml) was hydrogenated over Raney nickel (10 ml) at room temperature under ordinary pressure. After about 2.3 l of H_2 had been absorbed, the catalyst was filtered off and the filtrate was concentrated. The residue was chromatographed on silica gel with MeOH–$CHCl_3$ (1: 1) to afford the crude **7**, which was washed with ether. The crude **7**, was purified by column chromatography on alumina using $CHCl_3$ to give **7** (10 g). NMR ($CDCl_3$) δ: 2.24 (3H, s, $-\overset{|}{N}-CH_3$), 2.32 (6H, s, $C_{2,6}-CH_3$), 2.68 (2H, t, $-CH_2C\underline{H}_2\overset{|}{N}-$), 3.56 (2H, s, $-C\underline{H}_2C_6H_5$), 3.67 (3H, s, $-COOCH_3$), 4.24 (2H, t, $-COOC\underline{H}_2CH_2-$), 5.00 (1H, s, C_4-H), 5.92 (1H, s, $-\overset{|}{N}H$), 6.60, 7.00 (eah 3H, 1H, both m, C_4-aromatic protons), 7.36 (5H, s, $-CH_2C_6\underline{H}_5$). MS *m/e*: 449 (M^+).

Methyl 2-(N-Methylamino)ethyl (*m*-Aminophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (8) (M-3)——**7** (6.5 g) in MeOH (40 ml) was catalytically hydrogenated in the presence of 10% Pd–C (1.5 g) at room temperature under ordinary pressure (H_2 uptake, about 350 ml). The catalyst was removed and the solvent was evaporated off. The oily residue was triturated with ether and dissolved in a small amount of $CHCl_3$–MeOH (1: 1). The solution was applied to a column of alumina which was eluted with $CHCl_3$–MeOH (10: 1) to yield **8** (3 g). NMR ($CDCl_3$) δ: 2.28 (3H, s, $-NH-C\underline{H}_3$), 2.34 (6H, s, $C_{2,6}-CH_3$), 2.72 (2H, m, $-CH_2-C\underline{H}_2NH-$), 3.66 (3H, s, $-COOCH_3$), 4.04, 4.26 (each 1H, both m, $-COOC\underline{H}_2CH_2-$), 4.90 (1H, s, C_4-H), 5.93 (1H, s, dihydropyridine ring $-\overset{|}{N}H$), 6.60, 7.00 (each 3H, 1H, both m, C_4-aromatic protons). MS *m/e*: 359 (M^+).

2-(N-Benzyl-N-methylamino)ethyl Methyl 2,6-Dimethyl-4-(*m*-nitrophenyl)pyridine-3,5-dicarboxylate (9) (M-5)——**6** (10 g) was warmed with 2 N nitric acid (60 ml) to 60°. The temperature was kept at 55—60° by cooling with cold water during the vigorous reaction. When the reaction had subsided, the reaction mixture was stirred at the same temperature for 15 min and extracted with $CHCl_3$. The extract was washed with water, 15% aqueous K_2CO_3, and again with water, and then dried over $MgSO_4$. After removal of the solvent, the resulting yellow oil (8.0 g) was purified by column chromatography on alumina ($CHCl_3$–acetone (1: 1)) to give **9** (6 g). NMR ($CDCl_3$) δ: 2.12 (3H, s, –N–CH_3), 2.40 (2H, t, –CH_2C$\underline{H_2}$N–), 2.64 (6H, s, $C_{2,6}$–CH_3), 3.44 (2H, s, –C$\underline{H_2}C_6H_5$), 3.52 (3H, s, –$COOCH_3$), 4.08 (2H, t, –COOC$\underline{H_2}CH_2$–), 7.23 (5H, s, –$CH_2C_6\underline{H_5}$), 7.52—8.14 (4H, m, C_4-aromatic protons). MS *m/e*: 477 (M^+).

Methyl 2-(N-Methylamino)ethyl 4-(*m*-Aminophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (10) (M-4)——**9** (6.5 g) in MeOH (30 ml) was reduced catalytically (10% Pd-C (2.0 g)) at room temperature under ordinary pressure (H_2 uptake, about 1.3 l). The reaction mixture was filtered and concentrated. $CHCl_3$ was added to the residue and the undissolved material was filtered off. The filtrate was concentrated to afford the crude product (3.0 g), which, after column chromatography on alumina ($CHCl_3$–MeOH (50: 1)), afforded pure **10** (2.1 g). NMR ($CDCl_3$) δ: 2.28 (3H, s, –NH–C$\underline{H_3}$), 2.52 (2H, t, –C$\underline{H_2}$NH–), 2.58, 2.60 (each 3H, both s, $C_{2,6}$–CH_3), 3.59 (3H, s, –$COOCH_3$), 4.16 (2H, –COOC$\underline{H_2}CH_2$–), 6.63, 7.19 (each 3H, 1H, both m, C_4-aromatic protons). MS *m/e*: 357 (M^+).

Dimethyl 2,6-Dimethyl-4-(*m*-nitrophenyl)pyridine-3,5-dicarboxylate (12)——**12** (8.5 g) was prepared from dimethyl 2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate[8] **11** (10 g), by a method similar to that described by Cook *et al.*[7] NMR (d_6-DMSO) δ: 2.57 (6H, s, $C_{2,6}$–CH_3), 3.58 (6H, s, –$COOCH_3$), 7.7—8.6 (4H, m, C_4-aromatic protons).

2,6-Dimethyl-5-methoxycarbonyl-4-(*m*-nitrophenyl)pyridine-3-carboxylic Acid (13) (M-6)——**12** (10 g) obtained above was added to a solution of KOH (1.92 g) in MeOH (50 ml). The mixture was refluxed for 18 hr. After cooling, cold water (250 ml) was added to the reaction mixture and unreacted starting material was extracted with $CHCl_3$. The aqueous layer was acidified to pH 2 with 1 N HCl and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and concentrated. The residual solid was recrystallized from MeOH to yield crystals of **13** (5.5 g) mp 196—198°. NMR (d_6-DMSO) δ: 2.49, 2.54 (each 3H, both s, $C_{2,6}$-CH_3), 3.48 (3H, s, $COOCH_3$), 7.60—8.50 (4H, m, C_4-aromatic protons). MS *m/e*: 330 (M^+). *Anal.* Calcd for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27; N, 8.48. Found: C, 57.68; H, 4.22; N, 8.27.

5-Methoxycarbonyl-2,6-dimethyl-4-(*m*-nitrophenyl)pyridine-3-carboxylic Acid N-Oxide (14)——A solution of **13** (20 g) and 40% peracetic acid (16.4 g) in EtOH (200 ml) was refluxed for 3.5 hr. The reaction mixture was concentrated to *ca.* 30 ml. After addition of water (30 ml), the solution was extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and concentrated. A small volume of ether was added to the residue to give the N-oxide (**14**) (17.5 g) as crystals, mp 194—200°. NMR (d_6-DMSO) δ: 2.33, 2.38 (each 3H, both s, $C_{2,6}$-CH_3), 3.42 (3H, s, –$COOCH_3$), 7.20—8.10 (4H, m, C_4-aromatic protons). MS *m/e*: 346 (M^+).

3-Methoxycarbonyl-2-methyl-4-(*m*-nitrophenyl)-5-oxo-5,7-dihydrofuro[3,4-*b*]pyridine (16) (M-8)——A mixture of **14** (15 g) and acetic anhydride (5.32 g) was heated at 140° for 5 min. The reaction mixture was concentrated and dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water and concentrated. The residue was dissolved in MeOH (50 ml), followed by addition of a solution of KOH (2.8 g) in MeOH (100 ml). The solution was refluxed for 5 min and evaporated to dryness. After addition of 6 N HCl (300 ml), the residue was heated (bath temperature 90—100°) for 2 hr. The remaining insoluble material was filtered off. The filtrate was diluted with water (300 ml) to afford a solid, which was chromatographed on silica gel with AcOEt. After concentration of the eluate, the solid obtained was washed with ether and recrystallized from acetone to give **16** (3.5 g) in crystalline form, mp 200—202°. IR ν_{max}^{KBr} cm^{-1}: 1767 (C=O of lactone). NMR (d_6-DMSO) δ: 2.67 (3H, s, C_2–CH_3), 3.61 (3H, s, –$COOCH_3$), 5.43 (2H, s, –CH_2OCO–), 7.70—8.50 (4H, m, C_4-aromatic protons). MS *m/e*: 328 (M^+). *Anal.* Calcd for $C_{16}H_{12}N_2C_6$: O, 58.54; H, 3.68; N, 8.53. Found: C, 57.98; H, 3.59; N, 8.40.

Ethoxycarbonylmethyl Methyl 2,6-Dimethyl-4-(*m*-nitrophenyl)pyridine-3,5-dicarboxylate (17)——Na (0.7 g) was dissolved in dry MeOH (100 ml). Next, **13** (10 g) and ethyl bromoacetate (5.06 g) were added, and the mixture was heated under reflux for 4.5 hr. After removal of the solvent, cold water (30 ml) was added to the residue and the solution was extracted with $CHCl_3$. The extract was washed with ice-cooled 1 N NaOH and water, dried over Na_2SO_4 and concentrated to yield **17** (9.3 g). NMR (d_6-DMSO) δ: 1.14 (3H, t, –$COOCH_2C\underline{H_3}$), 2.54, 2.63 (each 3H, both s, $C_{2,6}$–CH_3), 3.52 (3H, s, –$COOCH_3$), 4.07 (2H, q, –COOC$\underline{H_2}$-CH_3), 4.61 (2H, s, –$COOCH_2COO$–), 7.50—8.50 (4H, m, C_4-aromatic protons). MS *m/e*: 416 (M^+).

Carboxymethyl Methyl 2,6-Dimethyl-4-(*m*-nitrophenyl)pyridine-3,5-dicarboxylate (18) (M-9)——**17** (9.3 g) was added to a solution of KOH (1.57 g) in MeOH (90 ml). The mixture was stirred at room temperature for 3 hr and heated to 70°. It was then cooled rapidly and concentrated. After addition of cold water, unreacted starting material was removed by extraction with $CHCl_3$. Usual work-up gave a solid product which was recrystallized from MeOH to afford **18** (1.7 g) as crystals, mp 198—202°. NMR (d_6-DMSO) δ: 2.56, 2.65 (each 3H, both s, $C_{2,6}$–CH_3), 3.55 (3H, s, –$COOCH_3$), 4.56 (2H, s, –$COOCH_2COO$–), 7.50—8.50 (4H, m, C_4-aromatic protons). MS *m/e*: 388 (M^+). *Anal.* Calcd for $C_{18}H_{16}N_2O_8$: C, 55.67; H, 4.15; N, 7.21. Found: C, 55.84; H, 4.19; N, 7.30.