Synthesis of 4-Chloro-7-ethoxy-2(3*H*)-benzoxazolone-6-carboxylic Acid

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As a part of metabolic studies of mosapride (**1**), a potential gastroprokinetic agent, the synthesis of 4-chloro-7-ethoxy-2(3*H*)-benzoxazolone-6-carboxylic acid (**7**) as a derivative of 4-amino-5-chloro-2-ethoxy-3-hydroxybenzoic acid (**6**), which has served a benzoic acid part of the metabolites **4** and **5**, is described. Treatment of methyl 3-amino-4-substituted amino-5-chloro-2-ethoxybenzoate derivatives **11a-c** with sodium nitrate in acidic medium gave the benzotriazole derivatives **13x,y** instead of the objective 3-hydroxy counterpart. The synthesis of **7** started from *o*-vanillin acetate (**15**) and proceeded through the intermediates 2-hydroxy-3-methoxy-4-nitrobenzaldehyde (**18**), methyl 4-amino-2,3-dihydroxybenzoate (**23**), and methyl 7-hydroxy-2(3*H*)-benzoxazolone-6-carboxylate (**30**). Compound **30** was alternatively prepared from **23** *via* methyl 4-ethoxycarbonylamino-2-ethoxycarbonyloxy-3-hydroxybenzoate (**29**), which is the product resulting from the migration of the ethoxycarbonyl group of methyl 4-amino-2,3-diethoxycarbonyloxybenzoate (**27**).

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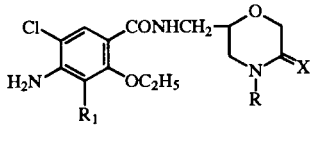
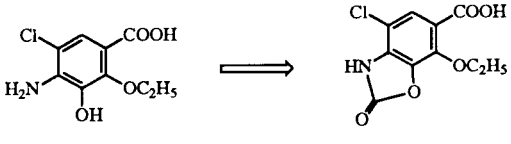
Mosapride [4-amino-5-chloro-2-ethoxy-*N*-{[4-(4-fluorobenzyl)-2-morpholinyl]methyl}benzamide, **1** is a new and potent gastroprokinetic agent without dopamine D_2 receptor antagonistic activity, which is presently under clinical studies [1–3]. It acts as a partial agonist for a serotonin-4 receptor [4]. During the metabolic studies of **1**, four metabolites were isolated from rat urine, and their structures were proposed to be the des 4-fluorobenzylated mosapride **2**, its oxo analogue **3**, and the corresponding 3-hydroxylated compounds **4** and **5** (Figure 1) on the basis of their ^{1}H-nmr and ms spectra [5]. The structures of metabolites **2** and **3** were confirmed by means of comparison with the synthetic compounds [6]. In order to confirm the proposed the structures of two metabolites **4** and **5**, the common intermediate, 4-amino-5-chloro-2-ethoxy-3-hydroxybenzoic acid (**6**) or its derivative with the protection of 4-amino and/or 3-hydroxy groups became essential. We describe the synthetic trial of compound **6** *via* the corresponding 3-diazonium derivatives and the preparation of the 4-chloro-7-ethoxy-2(3*H*)-benzoxazolone-6-carboxylic acid (**7**) as a protected compound of both 4-amino and 3-hydroxy groups of **6**.



1, R = 4-FC$_6$H$_4$CH$_2$, R$_1$ = H, X = H$_2$ (mosapride)
2, R = H, R$_1$ = H, X = H$_2$
3, R = H, R$_1$ = H, X = O
4, R = H, R$_1$ = OH, X = H$_2$
5, R = H, R$_1$ = OH, X = O



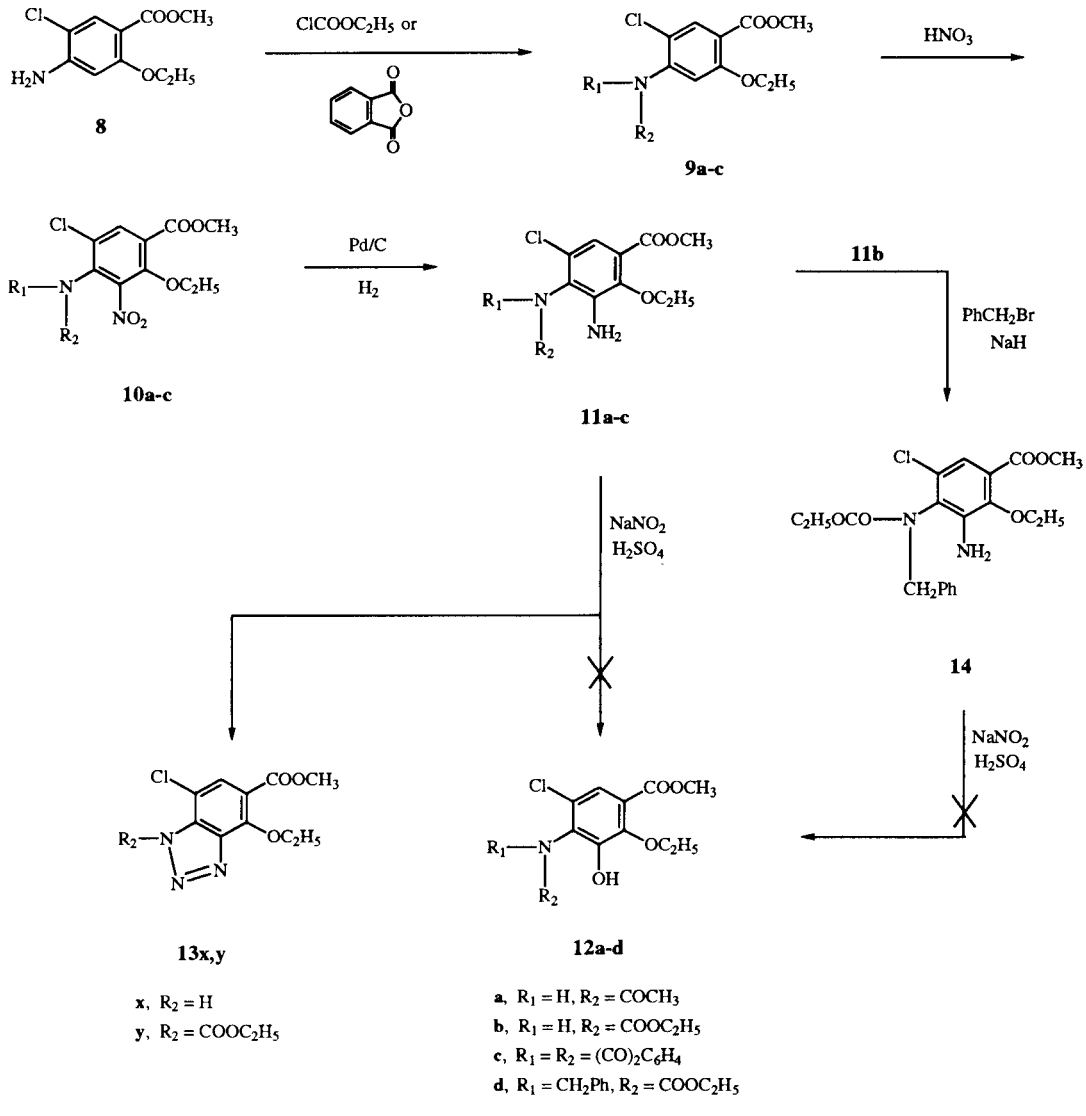
6 **7**

Figure 1

To our knowledge, the only literature procedure for the preparation of methyl 3-hydroxy-2-alkoxy-4-acetylamino-5-chlorobenzoate *via* the corresponding 3-diazonium intermediate is a recent report by the Beecham group [7]. Thus, the reaction of methyl 3-amino-4-acetylamino-5-chloro-2-methoxybenzoate with sodium nitrate in 25% aqueous sulfuric acid solution afforded the corresponding 3-hydroxy counterpart, which is the intermediate of serotonin-3 receptor antagonists. We accordingly applied this method. When the literature reaction was repeated on methyl 3-amino-4-acetylamino-5-chloro-2-ethoxybenzoate (**11a**), which was obtained by nitration of methyl 4-acetylamino-5-chloro-2-ethoxybenzoate (**9a**) [1], followed by reduction of the resultant 3-nitro derivative **10a**, the benzotriazole **13x** was obtained in a good yield instead of the desired 3-hydroxyester **12a**. Reexamination of this reaction led to different result.

Next, the similar reaction of **11b** with ethoxycarbonyl group instead of acetyl group as a protected group of **11a** was examined. Compound **11b** was prepared as follows. Treatment of **8** [1] with ethyl chloroformate, followed by nitration of the resultant **9b** and subsequent reduction of the 3-nitro compound **10b**, furnished the 3-amino derivative **11b**. The reaction of **11b** also caused the same result to afford the benzotriazole analogue **13y** instead of **12b** in a good yield. To avoid formation of benzotriazole ring, compounds **11c** and **14** with 4-disubstituted amino group were selected as a starting material. The 4-phthalimido analogue **11c** was prepared from **9c** *via* the 3-nitroester **10c**. Compound **14** was obtained by treatment of **11b** with benzyl bromide in the presence of sodium hydride. The similar diatization of both compounds **11c** and **14** was carried out, but the corresponding 3-hydroxy products **12c** and **12d** were not obtained. As a result, the method of the Beecham group is not easily reproducible (Scheme 1).

Scheme I



We planned a new procedure for the preparation of the 3-hydroxy derivative; *o*-vanillin acetate (**15**) [8] as a starting material was selected and stepwise synthesis of **6** or **7** was carried out. Piatak *et al.* [9] reported that treatment of **15** with fuming nitric acid in concentrated sulfuric acid at -15° and subsequent alkaline hydrolysis of the 2-acetoxy group gave 2-hydroxy-3-methoxy-4-nitrobenzaldehyde (**18**) in a good yield. We prepared **18** using a modification of the procedure reported by Piatak *et al.* Compound **15** was treated with fuming nitric acid in concentrated sulfuric acid at -40° afforded the mixture of the desired 2-formyl-6-methoxy-5-nitrophenyl acetate (**16**) and the corresponding hydroxy analogue **18** along with a mixture of the regioisomers **17** and **19**. After separation of **16/18** and **17/19** using column chromatography, each mixture was hydrolyzed in alkaline solution to furnish compounds **18** and **19**. The position of the nitro group of **18** and **19** was determined by nuclear Overhauser effect (NOE) experiments. In the difference NOE spectra of **18** and **19**, irradiations at δ 10.00 (CHO) of **18** and δ 4.02 (OCH_3) of **19** enhanced the signal intensities of the aromatic 6-proton (δ 7.45) of **18** and of the aromatic 4-proton (δ 7.05) of **19**, respectively. However, NOEs were not observed at the aromatic protons on irradiations at δ 4.07 (OCH_3) of **18** and at δ 10.51 (CHO) of **19** (Figure 2). Based on the above evidence, the structures of **18** and **19** were characterized as 2-hydroxy-3-methoxy-4-nitrobenzaldehyde and 2-hydroxy-3-methoxy-6-nitrobenzaldehyde, respectively. The aldehyde **18** was oxidized on treating potassium permagunesium to give the salicylic acid **20**. Reaction of **20** with hydrobromic acid, followed by hydrogenation of the 4-nitro group of the resultant 2,3-hydroxybenzoic acid **21**

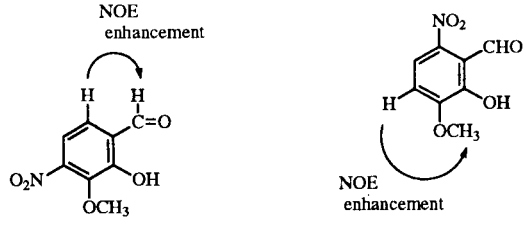
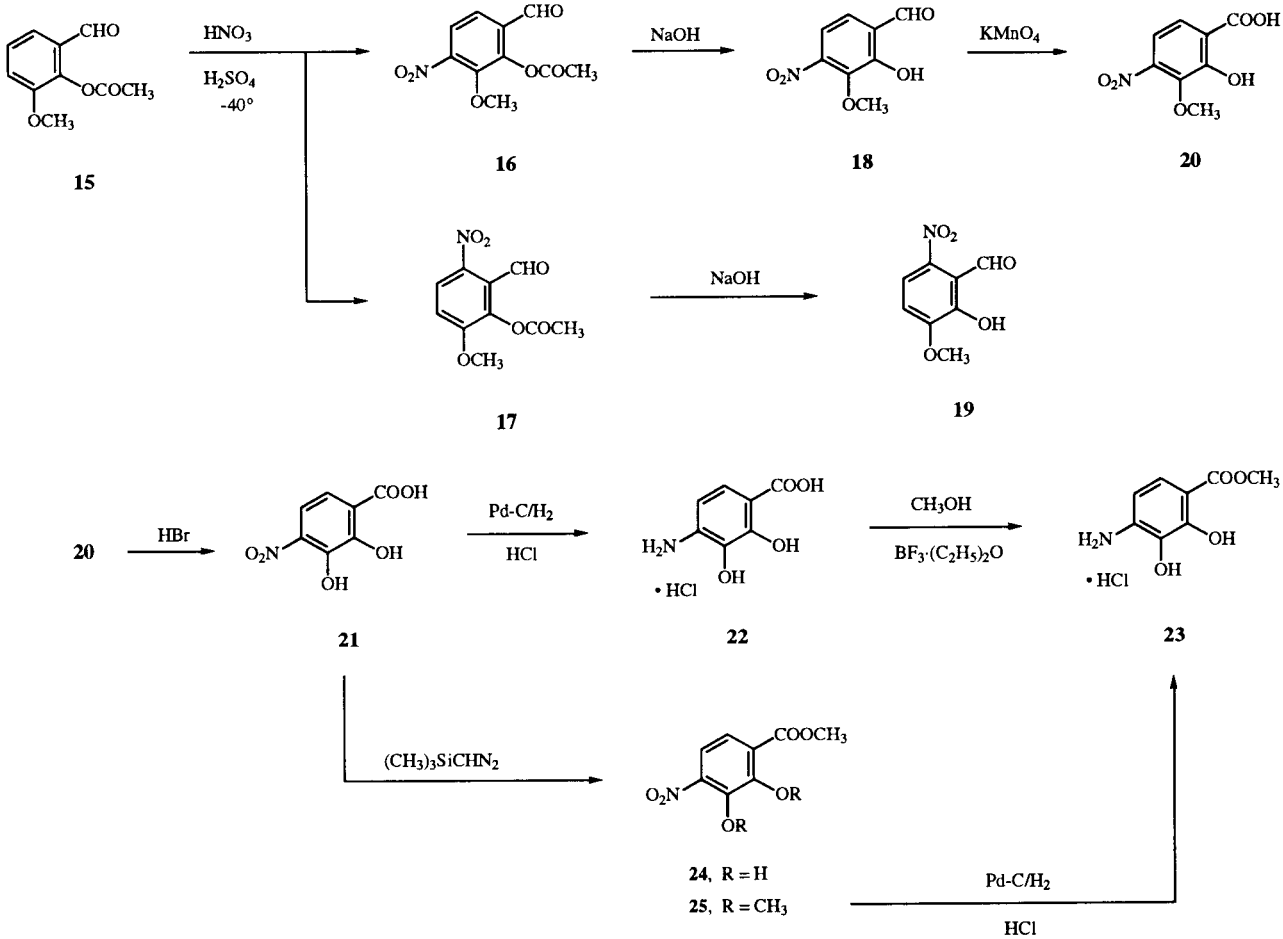


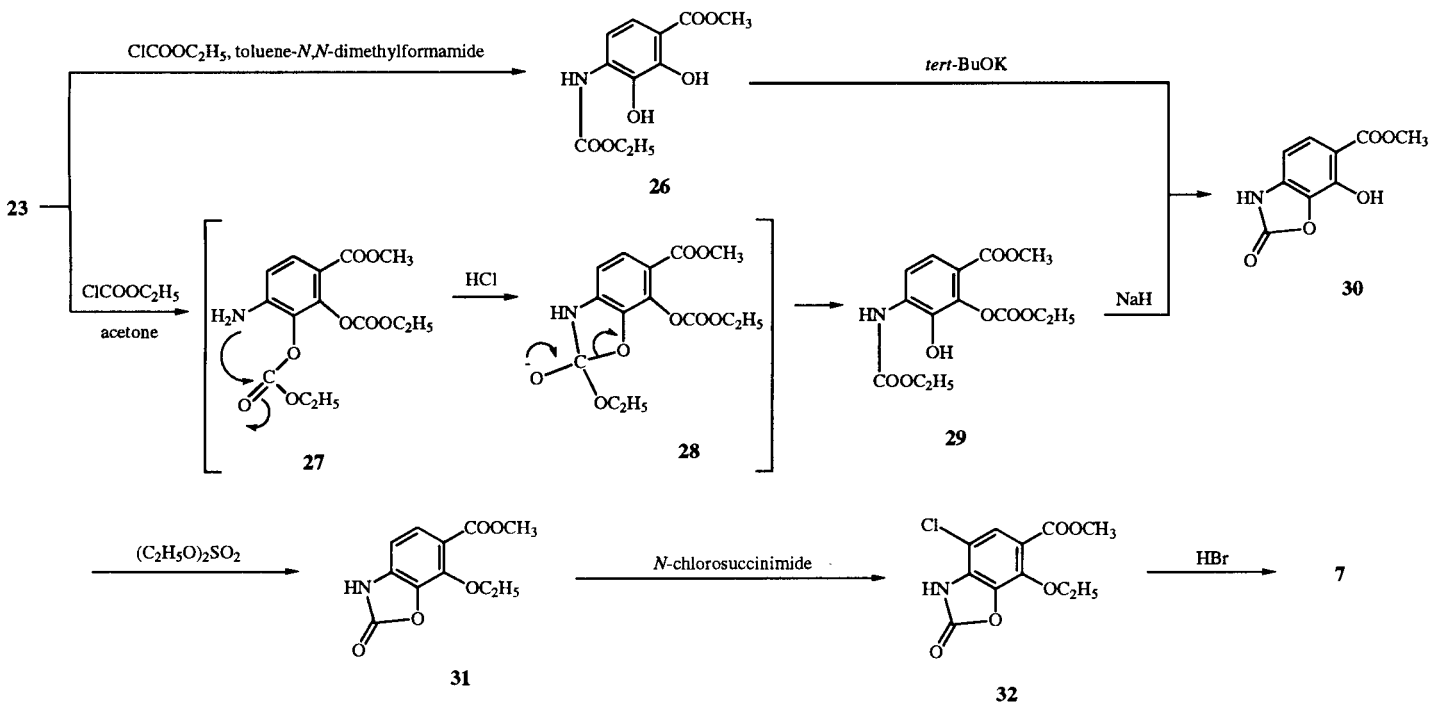
Figure 2

in the presence of hydrochloric acid, produced 4-amino-2,3-dihydroxybenzoic acid hydrochloride (**22**). Subsequent esterification of **22** to **23** in methyl alcohol in the presence of catalytic concentrated sulfuric acid did not proceed, and unreacted **22** was recovered. Esterification using boron trifluoride etherate as an acid gave the target **23** in 70% yield, although prolonged reaction time was necessary (65 hours). To gain the methyl ester counterpart **24** of **21**, on the other hand, reaction of **21** with diazomethane was carried out, but the 2,3-dimethoxyester **25** instead of the desired **24** was isolated as a product. Treatment of **21** with (trimethylsiliy)diazomethane (*ca.* 4 molar equivalent) gave the methyl ester **24**, which was transformed smoothly into the corresponding ester **23** in only 25% yield (Scheme II). Treatment of the 4-aminoester **23** with ethyl chloroformate in a mixture of toluene-*N*,*N*-dimethylformamide produced the 4-ethoxycarbonylamino-ester **26**, which was cyclized on treating potassium *tert*-butoxide to give the benzoxazole derivative **30** in 28% overall yield. In the reaction of **23** with ethyl chloroformate, on the other hand, use of acetone as a solvent gave the 2,3-diethoxycarbonyloxy ester **27** in a good yield, but compound **26** did not detect it. Compound **27** was treated with hydrochloric acid to give the 4-ethoxycarbonylamino-3-hydroxyester **29** in an excellent yield. The reaction included the migration of the ethoxycarbonyl group at the 3-position to the 4-amino group as shown **28** in Scheme III. Treatment of **29** with sodium hydride caused not only the cyclization to the benzoxazolone ring but the concurrent deethoxycarbonylation at the 2-position, thereby affording compound **28** in 66% overall yield from

Scheme II



Scheme III



23. This compound was confirmed to be identical with the sample prepared from **26**, on the basis of the spectral data. The benzoxazolone **30** was treated with diethyl sulfate to give the 2-ethoxy derivative **31**. Chlorination of **31** with *N*-chlorosuccinimide, followed by acid hydrolysis using hydrobromic acid of the resultant **32**, afforded the requisite benzoic acid **7**. Unfortunately, various attempted condensations of **7** with the 2-aminomethyl-5-oxomorpholine [6] which is common amine part of the metabolites **3** and **5** *via* the corresponding acid chloride or anhydride and using the coupling reagents were completely unsuccessful, although the reason for this observation could not be explained.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro melting point apparatus without correction. The ir spectra were recorded on a Hitachi 260-10 spectrometer with potassium bromide disks unless otherwise specified. Electron ionization (EI) and secondary ion (SI) mass spectra were obtained on a JEOL JMS D-300 or a Hitachi M-80B spectrometer. The ^{1}H-nmr spectra were taken at 200 MHz with a Varian Gemini-200 spectrometer unless otherwise specified. The ^{1}H-nmr spectra (300 MHz) were recorded on a Varian XL-300 spectrometer. Chemical shifts are expressed as δ (ppm) values with tetramethylsilane as an internal standard, and coupling constants (J) are given in hertz (Hz). Organic extracts were dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. Merck silica gel 60 (70-230 mesh) was used for column chromatography.

Methyl 5-Chloro-2-ethoxy-4-ethoxycarbonylaminobenzoate (**9b**).

A mixture of methyl 4-amino-5-chloro-2-ethoxybenzoate [1] (**8**, 50.7 g, 0.22 mole), ethyl chloroformate (59.9 g, 0.55 mole), 4-dimethylaminopyridine (1.0 g), pyridine (60 ml), and toluene (1000 ml) was heated to reflux for 18 hours. The reaction mixture was poured into ice-water and acidified with 35% aqueous hydrochloric acid. The organic layer was separated and washed successively with water and brine. The solvent was evaporated to leave a residue, which was crystallized from toluene to give 65.5 g (95%) of **9b**, mp 80-81°; ir: 3400, 2970, 1725, 1690, 1565, 1200 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.35 (t, J = 7.0, 3H, CH_2CH_3), 1.47 (t, J = 7.0, 3H, CH_2CH_3), 3.86 (s, 3H, $COOCH_3$), 4.16 (q, J = 7.0, 2H, CH_2CH_3), 4.26 (q, J = 7.0, 2H, CH_2CH_3), 7.28 (br s, 1H, NHCO), 7.86 (s, 1H, arom 3-H), 8.02 (s, 1H, arom 6H); ms: (EI) m/z 301 (M^+).

Anal. Calcd. for $C_{13}H_{16}ClNO_5$: C, 51.75; H, 5.35; N, 4.64. Found: C, 51.82; H, 5.32; N, 4.56.

Methyl 5-Chloro-2-ethoxy-4-phthalimidobenzoate (**9c**).

A mixture of **8** (45.9 g, 0.20 mole) and phthalic anhydride (44.4 g, 0.30 mole) was heated at 150° for 3 hours and then cooled to room temperature. The reaction mixture was chromatographed on silica gel with chloroform to give an oily residue, which was crystallized from toluene-hexane to afford 67.5 g (94%) of **9c**, mp 139-142°; ir: 2975, 2930, 1775, 1710, 1360, 1230 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.46 (t, J = 7.0, 3H, CH_2CH_3), 3.92 (s, 3H, $COOCH_3$), 4.11 (q, J = 7.0, 2H, CH_2CH_3), 6.95 (s, 1H, arom 3-H), 7.75-7.9 (m, 2H), 7.9-8.05 (m, 3H); ms: (SI) m/z 360 (MH^+), 328, 300.

Anal. Calcd. for $C_{18}H_{14}ClNO_5$: C, 60.09; H, 3.92; N, 3.89. Found: C, 60.11; H, 3.80; N, 3.79.

Methyl 4-Acetylamino-5-chloro-2-ethoxy-3-nitrobenzoate (**10a**).

To a solution of fuming nitric acid (*d* 1.52, 350 ml) and concentrated sulfuric acid (40 ml) was added portionwise **9a** [1] (120.0 g, 0.44 mole) kept at -10°. The mixture was stirred at the same temperature for 5 minutes, poured into ice-water, and then extracted with chloroform. The extract was washed successively with water, 10% aqueous sodium bicarbonate solution, water, and brine. The solvent was evaporated to leave a solid, which was recrystallized from toluene to give 106.5 g (76%) of **10a**, mp 137-138°; ir: 3220, 2975, 1725, 1705, 1670, 1530, 1375, 1245 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.38 (t, J = 7.0, 3H, CH_2CH_3), 2.20 (s, 3H, $COCH_3$), 3.95 (s, 3H, $COOCH_3$), 4.18 (q, J = 7.0, 2H, CH_2CH_3), 7.28 (br s, 1H, NHCO), 8.08 (s, 1H, arom 6-H); ms: (SI) m/z 317 (MH^+), 275, 243.

Anal. Calcd. for $C_{12}H_{13}ClN_2O_6$: C, 45.51; H, 4.14; N, 8.85. Found: C, 45.56; H, 4.05; N, 8.68.

In a similar manner to that described above, compounds **10b** and **10c** were prepared from **9b** and **9c**, respectively. Yield, melting point, spectral data, and elemental analysis are given below.

Methyl 5-Chloro-2-ethoxy-4-ethoxycarbonylamino-3-nitrobenzoate (**10b**).

This compound was obtained in 68% yield, mp 87-89° (toluene-hexane); ir: 3225, 2970, 1720, 1700, 1530, 1365, 1235 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.30 (t, J = 7.0, 3H, CH_2CH_3), 1.39 (t, J = 7.0, 3H, CH_2CH_3), 3.95 (s, 3H, $COOCH_3$), 4.17 (q, J = 7.0, 2H, CH_2CH_3), 4.23 (q, J = 7.0, 2H, CH_2CH_3), 6.72 (br s, 1H, NHCO), 8.07 (s, 1H, arom 6-H); ms: (SI) m/z 347 (MH^+), 315, 243, 215.

Anal. Calcd. for $C_{13}H_{15}ClN_2O_7$: C, 45.03; H, 4.36; N, 8.08. Found: C, 45.01; H, 4.30; N, 7.94.

Methyl 5-Chloro-2-ethoxy-3-nitro-4-phthalimidobenzoate (**10c**).

This compound was obtained in 76% yield, mp 156-157° (toluene-hexane); ir: 2975, 1785, 1730, 1535, 1365, 1340, 1245 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.40 (t, J = 7.0, 3H, CH_2CH_3), 3.99 (s, 3H, $COOCH_3$), 4.22 (q, J = 7.0, 2H, CH_2CH_3), 7.8-7.9 (m, 2H), 7.95-8.05 (m, 2H), 8.18 (s, 1H, arom 6-H); ms: (EI) m/z 404 (M^+), 298.

Anal. Calcd. for $C_{18}H_{13}ClN_2O_7$: C, 53.41; H, 3.24; N, 6.92. Found: C, 53.27; H, 3.13; N, 6.89.

Methyl 4-Acetylamino-3-amino-5-chloro-2-ethoxybenzoate (**11a**).

A solution of **10a** (30.0 g, 95 mmoles) in a mixture of ethyl acetate (200 ml) and 10% aqueous ethyl alcohol (200 ml) was hydrogenated with wet Raney nickel (*ca.* 3 g) at room temperature at 4.0 kg/cm^2. After no further change was observed on the pressure of hydrogen (*ca.* 1 hour), the catalyst was filtered through Celite. The filtrate was concentrated to dryness, and the residue was recrystallized from methyl alcohol-hexane to give 19.1 g (70%) of **11a**, mp 151-152°; ir: 3420, 3310, 3250, 2975, 1715, 1635, 1500, 1425, 1200 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.43 (t, J = 7.0, 3H, CH_2CH_3), 2.28 (s, 3H, $COCH_3$), 3.90 (s, 3H, $COOCH_3$), 4.02 (q, J = 7.0, 2H, CH_2CH_3), 4.52 (s, 2H, NH_2), 7.23 (br s, 1H, NHCO), 7.31 (s, 1H, arom 6-H); ms: (EI) m/z 286 (M^+), 184, 183.

Anal. Calcd. for $C_{12}H_{15}ClN_2O_4$: C, 50.27; H, 5.27; N, 9.77. Found: C, 50.32; H, 5.16; N, 9.63.

Methyl 3-Amino-5-chloro-2-ethoxy-4-ethoxycarbonylaminobenzoate (**11b**).

In a similar manner to that described above, **11b** was obtained from **10b** in 80% yield, mp 137-138° (ethyl alcohol); ir: 3420, 3330, 3280, 2975, 1725, 1670, 1530, 1430, 1290, 1200 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.32 (t, J = 7.0, 3H, CH_2CH_3), 1.43 (t, J = 7.0, 3H, CH_2CH_3), 3.90 (s, 3H, $COOCH_3$), 4.01 (q, J = 7.0, 2H, CH_2CH_3), 4.23 (q, J = 7.0, 2H, CH_2CH_3), 4.51 (s, 2H, NH_2), 6.43 (br s, 1H, NHCO), 7.31 (s, 1H, arom 6-H); ms: (SI) m/z 317 (MH^+), 316, 284, 256.

Anal. Calcd. for $C_{13}H_{17}ClN_2O_5$: C, 49.30; H, 5.41; N, 8.84. Found: C, 49.03; H, 5.36; N, 8.70.

Methyl 3-Amino-5-chloro-2-ethoxy-4-phthalimidobenzoate (**11c**).

A mixture of iron powder (17.3 g, 0.31 mole), ammonium chloride (6.6 g, 0.12 mole), and 50% aqueous ethyl alcohol (300 ml) was heated at *ca.* 80°, and **10c** (25.0 g, 62 mmoles) was added slowly and portionwise to the mixture at a such rate that the mild reflux was kept. After addition was completed, the whole was heated to reflux for an additional 1 hour. The resulting hot mixture was filtered through Celite. The filtrate was concentrated to leave an aqueous solution and extracted with chloroform. The extract was washed with brine and concentrated to leave a residue. The crude product was chromatographed on silica gel with ethyl acetate/hexane = 1/1 to give a pale yellow solid, which was recrystallized from ethyl alcohol to give 15.2 g (66%) of **11c**, mp 164-166°; ir: 3455, 3350, 2975, 2940, 1775, 1710, 1600, 1360, 1230 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.43 (t, J = 7.0, 3H, CH_2CH_3), 3.93 (s, 3H, $COOCH_3$), 4.06 (q, J = 7.0, 2H, CH_2CH_3), 4.18 (s, 2H, NH_2), 7.34 (s, 1H, arom 6-H), 7.75-7.9 (m, 2H), 7.9-8.05 (m, 2H); ms: (SI) m/z 375 (MH^+).

Anal. Calcd. for $C_{18}H_{15}ClN_2O_5$: C, 57.69; H, 4.03; N, 7.47. Found: C, 57.58; H, 3.90; N, 7.42.

The Diazotization of **11a** and **11b**.

a) A solution of **11a** (1.0 g, 3.5 mmoles) in concentrated sulfuric acid (20 ml) was poured into ice-water (50 g). To the solution was added dropwise a solution of sodium nitrate (0.4 g, 5.8 mmoles) in water (5 ml) at 5°. The mixture was stirred at room temperature for 15 hours. The resulting precipitates were collected by filtration, washed with water, and dried. The powder was recrystallized from toluene-hexane to give 0.7 g (78%) of methyl 7-chloro-4-ethoxy-1*H*-benzotriazole-5-carboxylate (**13x**), mp 143-144°; ir: 3175, 1709, 1612, 1500, 1440, 1380, 1355, 1230 cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 1.40 (t, J = 7.0, 3H, CH_2CH_3), 3.84 (s, 3H, $COOCH_3$), 4.84 (q, J = 7.0, 2H, CH_2CH_3), 7.77 (s, 1H, arom 6-H), 11.98 (br s, 1H, NH); ms: (SI): m/z 256 (MH^+).

Anal. Calcd. for $C_{10}H_{10}ClN_3O_3$: C, 46.98; H, 3.94; N, 16.44. Found: C, 46.78; H, 3.81; N, 16.37.

b) A solution of **11b** (1.0 g, 3.2 mmoles) in concentrated sulfuric acid (5 ml) was poured into a mixture of ice-water (50 g) and acetic acid (5 ml). To the solution was added dropwise a solution of sodium nitrate (0.3 g, 4.3 mmoles) in water (3 ml) at 5°. The mixture was stirred at the same temperature for 15 minutes. The resulting precipitate was collected by filtration, washed with water, and dried to give 0.7 g (68%) of methyl 7-chloro-4-ethoxy-1-ethoxycarbonyl-1*H*-benzotriazole-5-carboxylate (**13y**).

An analytical sample was obtained by recrystallization from ethyl alcohol-hexane, mp 75-77°; ir: 1775, 1765, 1718, 1480, 1222 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.54 (t, J = 7.0, 3H, CH_2CH_3), 1.56 (t, J = 7.0, 3H, CH_2CH_3), 3.94 (s, 3H, $COOCH_3$), 4.69 (q, J = 7.0, 2H, CH_2CH_3), 5.02 (q, J = 7.0, 2H, CH_2CH_3), 8.08 (s, 1H, arom 6-H); ms: (SI) m/z 328 (MH^+), 296 (M^+-OCH_3), 256, 224, 196.

Anal. Calcd. for $C_{13}H_{14}ClN_3O_5$: C, 47.64; H, 4.31; N, 12.82. Found: C, 47.35; H, 4.15; N, 12.87.

Methyl 3-Amino-4-(*N*-benzyl-*N*-ethoxycarbonyl)amino-5-chloro-2-ethoxybenzoate (**14**).

To a solution of **11b** (21.0 g, 66 mmoles) in anhydrous tetrahydrofuran (600 ml) was added portionwise sodium hydride (60% dispersion in mineral oil, 3.2 g, 80 mmoles) at *ca.* 5°. After the mixture was stirred at the same temperature for 30 minutes, benzyl bromide (11.9 g, 70 mmoles) was added. The reaction mixture was stirred at room temperature for 18 hours and concentrated to dryness. The residue was diluted with water and extracted with chloroform. The extract was washed with brine and evaporated to leave a residue. The crude product was chromatographed on silica gel with chloroform to give an oil, which was crystallized from toluene to afford 17.8 g (66%) of **14**, mp 93-94°; ir: 3400, 3325, 2975, 1725, 1680, 1300 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.13 (t, J = 7.0, 3H, CH_2CH_3), 1.32 (t, J = 7.0, 3H, CH_2CH_3), 3.70 (s, 2H, NH_2), 3.90 (s, 3H, $COOCH_3$), 3.90 (q, J = 7.0, 2H, CH_2CH_3), 4.14 (q, J = 7.0, 2H, CH_2CH_3), 4.28 (d, J = 14.5, 1H, $CH_2C_6H_5$), 5.15 (d, J = 14.5, 1H, $CH_2C_6H_5$), 7.22 (s, 1H, arom 6-H), 7.25 (s, 5H, C_6H_5); ms: (EI) m/z 406 (M^+).

Anal. Calcd. for $C_{20}H_{23}ClN_2O_5$: C, 59.04; H, 5.70; N, 6.89. Found: C, 59.07; H, 5.65; N, 6.77.

2-Hydroxy-3-methoxy-4-nitrobenzaldehyde (**18**).

The method of Piatak *et al.* [9] was applied. Finely powdered *o*-vanillin acetate [8] (**15**, 50.0 g, 0.26 mole) was added portionwise to a stirred solution of fuming nitric acid (*d* 1.52, 150 ml) and concentrated sulfuric acid (20 ml) kept at -40°. After the reaction mixture was stirred at the same temperature for *ca.* 5 minutes, and then immediately poured into ice-water. After the resultant oil was extracted with chloroform, and the extract was washed successively with water, 10% aqueous sodium bicarbonate solution, water, and brine. The solvent was evaporated to give an oil, which was chromatographed on silica gel with hexane/ethyl acetate = 4/1 to 3/2 to afford 40.1 g of a mixture of 2-formyl-6-methoxy-5-nitrophenyl acetate (**16**) and **18** as an oil and 9.0 g of a mixture of 2-formyl-6-methoxy-3-nitrophenyl acetate (**17**) and 2-hydroxy-3-methoxy-6-nitrobenzaldehyde (**19**) as a solid.

A mixture of compounds **16** and **18** had ^1H-nmr (deuteriochloroform): δ 2.47 (s, 3H, $COCH_3$), 3.99 (s, 3H, OCH_3 of **16**), 4.07 (s, 3H, OCH_3 of **18**), 7.29 (d, J = 8.5, 1H, arom 5-H of **18**), 7.45 (d, J = 8.5, 1H, arom 6-H of **18**), 7.72 (d, J = 8.5, 1H, arom 5-H of **16**), 7.76 (d, J = 8.5, 1H, arom 6-H of **16**), 10.0 (s, 1H, CHO of **18**), 10.1 (s, 1H, CHO of **16**), 11.4 (s, 1H, OH of **18**); ir (neat): 1770 ($OCOCH_3$), 1695 (CHO of **16**), 1655 (CHO of **18**), 1520, 1360 cm^{-1}.

A mixture of **16** and **18** (40.1 g) was hydrolyzed in a mixture of methyl alcohol (200 ml) and 2*N* aqueous sodium hydroxide solution (100 ml) by refluxing for 1 hour. The reaction mixture was concentrated to leave an aqueous solution, which was acidified with 35% aqueous hydrochloric acid. The resulting precipitates were collected by filtration, washed with water, and dried to give 37.1 g (73% yield from **15**) of **18** as a solid. An analytical sample was obtained by recrystallization from methyl alcohol-water, mp 90.5-91.5° [Lit [9] 92-93.5° (methyl alcohol-water), Lit [10] 89-92° (methyl alcohol-water)]; ^1H-nmr (300 MHz, deuteriochloroform): δ 3.89 (s, 3H, OCH_3), 7.43 (dd, J = 8.6, 0.6, 1H, arom 6-H), 7.59 (d, J = 8.6, 1H, arom 5-H), 10.30 (d, J = 0.6, 1H, CHO), 11.25 (s, 1H, OH); ir: 1665 (CHO), 1510, 1355 cm^{-1}.

Anal. Calcd. for $C_8H_7NO_5$: C, 48.74; H, 3.58; N, 7.10. Found: C, 48.62; H, 3.50; N, 7.06.

The fractional recrystallization of the solid (9.0 g) containing **17** and **19** from ethyl alcohol gave 6.0 g (10% yield from **15**) of **17**, mp 138-139°; ^1H-nmr (deuteriochloroform): δ 2.32 (s, 3H, $COCH_3$), 3.97 (s, 3H, OCH_3), 7.14 (d, J = 9.4, 1H, arom H), 8.18 (d, J = 9.4, 1H, arom H), 10.22 (s, 1H, CHO); ir: 1765 ($OCOCH_3$), 1690 (CHO) cm^{-1}.

Anal. Calcd. for $C_{10}H_9NO_6$: C, 50.22; H, 3.79; N, 5.86. Found: C, 50.25; H, 3.70; N, 5.83.

A mixture of **17** and **19** was hydrolyzed in a similar manner to that described above to give **19**. Compound **19** had mp 100-101° (ethyl alcohol-hexane); ^1H-nmr (300 MHz, deuteriochloroform): δ 4.02 (d, J = 0.3, 3H, OCH_3), 7.05 (dq, J = 8.9, 0.3, 1H, arom 4-H), 7.76 (d, J = 8.9, 1H, arom 5-H), 10.51 (d, J = 0.3, 1H, OH), 12.57 (dd, J = 0.8, 0.3, 1H, CHO); ir: 1640 (CHO), 1500, 1315 cm^{-1}.

Anal. Calcd. for $C_8H_7NO_5$: C, 48.74; H, 3.58; N, 7.10. Found: C, 48.74; H, 3.43; N, 7.03.

3-Methoxy-2-hydroxy-4-nitrobenzoic Acid (**20**).

A solution of potassium permanganate (64.2 g, 0.41 mole) in 50% aqueous acetone (1000 ml) was added to a solution of **18** (40.0 g, 0.20 mole) in acetone (3200 ml) at *ca.* 10°. The mixture was stirred at room temperature for 17 hours and then filtered through Celite. The filtrate was concentrated to leave an aqueous solution and acidified with 10% hydrochloric acid. The resulting precipitates were collected by filtration, washed with water, and recrystallized from methyl alcohol-water to give 17.3 g (40%) of **20**, mp 206-208° [Lit [9] 206.5-208° (methyl alcohol-water)]; ^1H-nmr (dimethyl sulfoxide-d_6): δ 3.92 (s, 3H, OCH_3), 7.33 (d, J = 9.0, 1H, arom 5-H), 7.70 (d, J = 9.0, 1H, arom 6-H), 11.0 (br s, 1H, HO); ir: 1660 (COOH), 1520, 1355 cm^{-1}.

Anal. Calcd. for $C_8H_7NO_6$: C, 45.08; H, 3.31; N, 6.57. Found: C, 45.12; H, 3.20; N, 6.57.

2,3-Dihydroxy-4-nitrobenzoic Acid (**21**).

A mixture of **20** (10.1 g, 47 mmoles), 47% aqueous hydrobromic acid (80 ml), and acetic acid (130 ml) was heated to reflux for 4 hours. After hplc analysis, the reaction mixture was cooled to *ca.* 5°. The resulting precipitate was collected by filtration, washed with water, and dried to give 8.8 g (93%) of **21**. An analytical sample was obtained by recrystallization from methyl alcohol-hexane, mp 202-205° [Lit [11] 194° (water), Lit [12] 208-210° (water)]; ^1H-nmr (dimethyl sulfoxide-d_6): δ 6.0 (br s, 2H, OH x 2), 7.31 (d, J = 9.0, 1H, arom 5-H), 7.36 (d, J = 9.0, 1H, arom 6-H), 10.4 (br s, 1H, COOH); ir: 3520, 3440, 1650 (COOH), 1520, 1330 cm^{-1}.

Anal. Calcd. for $C_7H_5NO_6$: C, 42.22; H, 2.53; N, 7.03. Found: C, 42.29; H, 2.38; N, 7.00.

Methyl 4-Amino-2,3-dihydroxybenzoate Hydrochloride (**23**).

(a) A mixture of **21** (20.0 g, 0.10 mole), 15% aqueous methyl alcohol (400 ml), and *ca.* 30% hydrochloric acid in ethyl alcohol

(18.3 g, *ca.* 0.15 mole) was hydrogenated with 10% palladium on carbon (1.0 g) at room temperature at 4.2 initial kg/cm^2. After no further change was observed on the pressure of hydrogen (*ca.* 1 hour), the catalyst was filtered through Celite and washed with methyl alcohol. The filtrate was evaporated to dryness. The residual solid was recrystallized from methyl alcohol-diethyl ether to give quantitative 20.6 g of 4-amino-2,3-dihydroxybenzoic acid hydrochloride (**22**), mp 180-181°; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 6.74 (d, J = 8.6, 1H, arom 5-H), 7.27 (d, J = 8.6, 1H, arom 6-H), 9.4 (br s, 6H, COOH, OH x 2, $NH_3^+Cl^-$); ir: 3450, 1662 (COOH) cm^{-1}; ms: (SI) m/z 170 (MH^+), 126 (MH^+-CO_2).

Anal. Calcd. for $C_7H_7NO_4$•HCl: C, 40.89; H, 3.92; N, 6.81. Found: C, 40.90; H, 3.89; N, 6.75.

A mixture of **22** (10.0 g, 49 mmoles), methyl alcohol (300 ml), and boron trifluoride etherate (5 ml) was heated to reflux for 65 hours. After hplc check, the reaction mixture was cooled to room temperature, and a proper amount of charcoal was added. The mixture was heated to reflux for 5 minutes, and the charcoal was filtered off. The filtrate was evaporated to leave a solid, which was triturated with acetone to give 7.5 g (70%) of **23**. An analytical sample was obtained by recrystallization from ethyl alcohol-diethyl ether, mp 165-168°; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 3.87 (s, 3H, $COOCH_3$), 6.58 (d, J = 9.0, 1H, arom 5-H), 7.26 (d, J = 9.0, 1H, arom 6-H), 8.12 (br s, 4H, OH, $NH_3^+Cl^-$) 10.7 (br s, 1H, OH); ir: 3410, 1660 ($COOCH_3$) cm^{-1}; ms: (SI) m/z 185 (MH^+).

Anal. Calcd. for $C_8H_9NO_4$•HCl: C, 43.75; H, 4.59; N, 6.38. Found: C, 43.53; H, 4.59; N, 6.44.

(b) (Trimethylsilyl)diazomethane [13] (2.0 *M* solution in hexane, 115 ml, 0.23 mole) was added to a solution of **21** (10.4 g, 52 mmoles) in a mixture of chloroform (200 ml) and methyl alcohol (300 ml) at room temperature. The mixture was stirred at room temperature for 1 hour and then concentrated to dryness. The residue was recrystallized from toluene-hexane to give 5.7 g (51%) of methyl 2,3-dihydroxy-4-nitrobenzoate (**24**). The mother liquid was concentrated to afford a solid, which was chromatographed on silica gel with chloroform/methyl alcohol = 9/1 to produce 0.6 g (5%) of methyl 2,3-dimethoxy-4-nitrobenzoate (**25**) as an oil and 2.8 g (25%) of **24** in this order of the elution.

Compound **24** had mp 95-97°; ir: 3175, 1675, 1515, 1325, 1220 cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 3.91 (s, 3H, $COOCH_3$), 7.31 (d, J = 9.0, 1H, arom 5-H), 7.39 (d, J = 9.0, 1H, arom 6-H), 10.81 (br s, 2H, OH x 2); ms: (SI) m/z 214 (MH^+).

Anal. Calcd. for $C_8H_7NO_6$: C, 45.08; H, 3.31; N, 6.57. Found: C, 45.06; H, 3.53; N, 6.45.

Compound **25** had ir (neat): 3090, 2995, 2940, 1725, 1520, 1460, 1400, 1350, 1300, 1240, 1030 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 3.96, 3.98, 4.03 (each s, each 3H, OCH_3 x 2, $COOCH_3$), 7.51 (d, J = 8.6, 1H, arom 5-H), 7.57 (d, J = 8.6, 1H, arom 6-H); ms: (SI) m/z 242 (MH^+), 210 (M^+-OCH_3).

A mixture of **24** (2.6 g, 12 mmoles), 10% aqueous methyl alcohol (150 ml), and *ca.* 30% hydrochloric acid in ethyl alcohol (1.8 g, *ca.* 15 mmoles) was hydrogenated with 10% palladium on carbon (0.4 g) at room temperature at 4.0 initial kg/cm^2. After no further change was observed on the pressure of hydrogen (*ca.* 1 hour), the catalyst was filtered through Celite and washed with methyl alcohol. The filtrate was evaporated to dryness. The residual solid was triturated with isopropyl alcohol-diisopropyl ether to give quantitative 2.7 g of **23**, which was identical with the sample described above, on the basis of ms, ir, and ^{1}H-nmr comparisons.

Methyl 7-Hydroxy-2(3*H*)-benzoxazolone-6-carboxylate (**30**).

(a) A mixture of **23** (2.8 g, 13 mmoles), triethylamine (4.0 g, 40 mmoles), 4-dimethylaminopyridine (0.2 g, 1.6 mmoles), ethyl chloroformate (2.1 g, 19 mmoles), toluene (100 ml), and *N*,*N*-dimethylformamide (20 ml) was heated to reflux for 2 hours. After the reaction mixture was cooled to *ca.* 5°, 10% aqueous hydrochloric acid (50 ml) was added. The organic layer was separated and washed with brine. The solvent was evaporated to leave a solid, which was chromatographed on silica gel with ethyl acetate/chloroform = 1/9 and then recrystallized from toluene to give 1.1 g (34%) of methyl 2,3-dihydroxy-4-ethoxycarbonylaminobenzoate (**26**), mp 151-154°; ir: 3398, 3325, 2950, 1720, 1650, 1510, 1435, 1290 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.33 (t, J = 7.2, 3H, CH_2CH_3), 3.93 (s, 3H, $COOCH_3$), 4.25 (q, J = 7.2, 2H, CH_2CH_3), 5.68 (s, 1H, 3-OH), 7.23 (br s, 1H, NHCO), 7.40 (dd, J = 8.8, 0.5, 1H, arom 5-H), 7.68 (d, J = 8.8, 1H, arom 6-H), 10.91 (s, 1H, 2-OH); ms: (SI) m/z 256 (MH^+), 224.

Anal. Calcd. for $C_{11}H_{13}NO_6$: C, 51.77; H, 5.13; N, 5.49. Found: C, 51.69; H, 5.12; N, 5.45.

A mixture of **26** (0.6 g, 2.4 mmoles), potassium *tert*-butoxide (0.3 g, 2.7 mmoles), and ethyl alcohol (40 ml) was heated to reflux for 2 hours and cooled to room temperature. The reaction mixture was concentrated to dryness. The residue was dissolved in chloroform and then washed successively with water and brine. The solvent was evaporated to leave a residual solid, which was chromatographed on silica gel with ethyl acetate/chloroform = 1/9 and then recrystallized from methyl alcohol to give 0.4 g (81%) of **30**, mp 286-288°; ir: 3210, 2950, 1750, 1730, 1670 cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 3.88 (s, 3H, $COOCH_3$), 6.72 (d, J = 8.8, 1H, arom 4-H), 7.66 (d, J = 8.8, 1H, arom 5-H), 10.77 (s, 1H, NHCO), 12.05 (br s, 1H, OH); ms: (SI): m/z 220 (MH^+).

Anal. Calcd. for $C_9H_7NO_5$: C, 51.68; H, 3.37; N, 6.70. Found: C, 52.02; H, 3.33; N, 6.47.

(b) To a suspension of **23** (60.2 g, 0.27 mole) in acetone (1000 ml) was added successively ethyl chloroformate (74.4 g, 0.69 mole) and triethylamine (138.5 g, 1.37 moles) at *ca.* 10°. The mixture was stirred at room temperature for 2.5 hours. After *ca.* 30% hydrochloric acid in ethyl alcohol (100 ml) was added to the reaction mixture containing methyl 4-amino-2,3-diethoxycarbonyloxybenzoate (**27**), the solution was heated to reflux for 18 hours and then cooled to room temperature. The reaction mixture was concentrated to dryness. The residue was diluted with water, extracted with chloroform, and washed with brine. The solvent was evaporated to give a solid, which was recrystallized from ethyl alcohol-hexane to afford 73.9 g (82% yield from **23**) of methyl 4-ethoxycarbonylamino-2-ethoxycarbonyloxy-3-hydroxybenzoate (**29**), mp 145-146°; ir: 3310, 2975, 1740, 1730, 1670, 1518, 1430, 1250 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.33 (t, J = 7.2, 3H, CH_2CH_3), 1.41 (t, J = 7.2, 3H, CH_2CH_3), 3.93 (s, 3H, $COOCH_3$), 4.26 (q, J = 7.2, 2H, CH_2CH_3), 4.38 (q, J = 7.2, 2H, CH_2CH_3), 7.07 (br s, 1H, OH), 7.71 (d, J = 8.8, 1H, arom 5-H), 7.78 (d, J = 8.8, 1H, arom 6-H), 11.06 (s, 1H, NHCO); ms: (SI) m/z 328 (MH^+), 296, 256, 224.

Anal. Calcd. for $C_{14}H_{17}NO_8$: C, 51.38; H, 5.24; N, 4.28. Found: C, 51.45; H, 5.02; N, 4.28.

To a solution of **29** (75.6 g, 0.23 mole) in tetrahydrofuran (2500 ml) was added portionwise sodium hydride (60% dispersion in mineral oil, 11.1 g, 0.28 mole) at *ca.* 10°. The mixture was heated to reflux for 18 hours, and recooled to room temperature. The solvent was evaporated to give a residue, which was dissolved in water and washed with chloroform. The aqueous solution was acidified with 35% aqueous hydrochloric acid. The resulting precipitates were collected by filtration, washed with water, and dried to give 38.7 g (80%) of **30**, which was confirmed to be identical with the sample from (a), on the basis of tlc, ir, ^{1}H-nmr, and ms comparisons.

In a preliminary experiment, the oily benzoate **27** was isolated and characterized; ir (neat): 3360, 2970, 1760, 1710, 1660, 1240 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.38 (t, J = 7.2, 3H, CH_2CH_3), 1.39 (t, J = 7.2, 3H, CH_2CH_3), 3.82 (s, 3H, $COOCH_3$), 4.24 (s, 2H, NH_2), 4.33 (q, J = 7.2, 2H, CH_2CH_3), 4.34 (q, J = 7.2, 2H, CH_2CH_3), 6.65 (d, J = 8.8, 1H, arom 5-H), 7.76 (d, J = 8.8, 1H, arom 6-H); ms: (SI) m/z 328 (MH^+), 296, 252, 224.

Methyl 7-Ethoxy-2(3*H*)-benzoxazolone-6-carboxylate (**31**).

A mixture of **30** (19.1 g, 91 mmoles), anhydrous potassium carbonate (18.9 g, 0.14 mole), diethyl sulfate (15.5 g, 0.10 mole), and *N,N*-dimethylformamide (300 ml) was heated at 80° for 3 hours. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with brine and concentrated to dryness. The residue was triturated with chloroform to give 15.2 g (70%) of **31**. An analytical sample was obtained by recrystallization from ethyl acetate-hexane, mp 183-184°; ir: 3020, 2940, 1750, 1670 cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 1.26 (t, J = 7.0, 3H, CH_2CH_3), 3.86 (q, J = 7.0, 2H, CH_2CH_3), 3.90 (s, 3H, $COOCH_3$), 6.96 (d, J = 8.8, 1H, arom 4-H), 7.71 (d, J = 8.8, 1H, arom 5-H), 10.78 (s, 1H, NHCO); ms: (SI) m/z 238 (MH^+).

Anal. Calcd. for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.58; H, 4.52; N, 5.82.

Methyl 4-Chloro-7-ethoxy-2(3*H*)-benzoxazolone-6-carboxylate (**32**).

A mixture of **31** (5.5 g, 23 mmoles), *N*-chlorosuccinimide (3.7 g, 28 mmoles), and *N,N*-dimethylformamide (50 ml) was heated at *ca.* 80° for 4 hours. The reaction mixture was poured into ice-water. The resulting precipitates were collected by filtration, washed with water, and recrystallized from acetone-hexane to give 3.4 g (54%) of **32**, mp 156-157°; ir: 3150, 3050, 1760, 1695 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.41 (t, J = 7.0, 3H, CH_2CH_3), 3.98 (s, 3H, $COOCH_3$), 4.22 (q, J = 7.0, 2H, CH_2CH_3), 7.70 (d, J = 8.8, 1H, arom 5-H), 10.87 (s, 1H, NHCO); ms: (SI) m/z 272 (MH^+).

Anal. Calcd. for $C_{11}H_{10}ClNO_5$: C, 48.64; H, 3.71; N, 5.16. Found: C, 48.63; H, 3.66; N, 5.07.

4-Chloro-7-ethoxy-2(3*H*)-benzoxazolone-6-carboxylic Acid (**7**).

A mixture of **32** (6.5 g, 24 mmoles), acetic acid (120 ml), and 47% aqueous hydrobromic acid (60 ml) was heated to reflux for 5 hours. After the reaction mixture was cooled to room temperature, the solution was concentrated. The resulting precipitates were collected by filtration, washed with water, and dried to give 5.2 g (84%) of **7** as a gray powder. An analytical sample was obtained by recrystallization from methyl alcohol-hexane, mp 243-244°; ir: 3070, 1735, 1685 cm^{-1}; ^{1}H-nmr (300 MHz, dimethyl sulfoxide-d_6): δ 1.43 (t, J = 7.0, 3H, CH_2CH_3), 4.71 (q, J = 7.0, 2H, CH_2CH_3), 7.79 (s, 1H, arom 5-H), 13.0 (br s); ms: (SI) m/z 258 (MH^+).

Anal. Calcd. for $C_{10}H_8ClNO_5$: C, 46.62; H, 3.13; N, 5.44. Found: C, 46.63; H, 3.01; N, 5.41.

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