Studies on Antidiabetic Agents. XII.[1] Synthesis and Activity of the Metabolites of (±)-5-[*p*-[2-(5-Ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (Pioglitazone)

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The metabolites of (±)-5-[*p*-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (1, pioglitazone), which is a representative insulin-sensitizing agent, were synthesized to confirm their structures and for studies of their pharmacological properties. Of the metabolites identified, a compound hydroxylated at the 2-position of the ethoxy chain (3) and compounds oxygenated at the ethyl side chain attached to the pyridine ring (4, 5) were found to be active, although the potency was slightly lower than that of the parent compound.

Key words antidiabetic agent; pioglitazone metabolite; 2,4-thiazolidinedione

In previous papers,[2–5] we reported on the potent hypoglycemic and hypolipidemic activity of pioglitazone (**1**) (AD-4833) in insulin-resistant animal models such as KKA^y mice[6] and Wistar fatty rats.[7] Plasma glucose, triglyceride and insulin concentrations decreased after several days of treatment with the compound.[3–5,8] The antidiabetic activity results from enhanced sensitivity of insulin-responsive tissues rather than increased release of insulin from islet β-cells. Pioglitazone is expected to effectively ameliorate glucose and lipid metabolic disturbances associated with non-insulin-dependent diabetes mellitus (NIDDM) and is currently under clinical evaluation.

Among the preclinical and clinical work, the metabolic fate and mechanism of action[9–13] have been studied in several animal species and in humans. The structures shown in Fig. 1 were proposed for the metabolites on the basis of spectroscopic analysis.[14] Syntheses of two of the metabolites, compounds **2** (M-I) and **3** (M-II), were reported previously.[2,15] Compounds M-III—V were herein prepared in order to unambiguously determine the structures and so that studies of the pharmacological properties of the metabolites could be carried out.

Compounds **4** (M-III), **5** (M-IV) and **6** (M-V) were synthesized starting from modified alcohols bearing a protected hydroxy moiety or a cyano moiety as a precursor of the carboxylic acid moiety described below. These compounds were tested for hypoglycemic and hypolipidemic activities using Wistar fatty rats.[7]

Synthesis of M-III and M-IV Protection of the hydroxy moiety of 5-(1-hydroxyethyl)-2-methylpyridine (**7**) as a methoxymethyl ether followed by hydroxymethylation with HCHO gave the 2-pyridylethanol (**8**), which was then condensed with *p*-fluoronitrobenzene to afford 2-(4-nitrophenoxy)ethyl]pyridine (**9**). Catalytic hydrogenation of the nitro moiety followed by the Meerwein arylation gave the 2-bromo-3-phenylpropionate (**10**). Reaction of **10** with thiourea afforded the corresponding 2-imino-4-thiazolidinone, which was not isolated, but subjected to concomitant acid hydrolysis of the 2-imino group on the thiazolidine ring and the methoxymethyl group at the ethyl side chain of the pyridine ring to obtain the desired M-IV. Oxidation of M-IV was effected by dimethyl sulfoxide (DMSO)–pyridine·SO_3 complex to give the corresponding acetyl derivative (M-III) (Chart 1).

Synthesis of M-V 5-Methoxymethoxymethyl-2-[2-(4-nitrophenoxy)ethyl]pyridine (**11**) was obtained by a similar method to that described for M-IV. The protected hydroxy moiety of **11** was converted to a cyano moiety, as a precursor of the carboxylic acid, by the usual method to afford 5-cyanomethyl-2-[2-(4-nitrophenoxy)ethyl]pyridine (**12**). The 2-imino-4-thiazolidinone derivative (**13**), which was prepared following the same method as used for M-IV, was hydrolyzed to the 2,4-thiazolidinedione

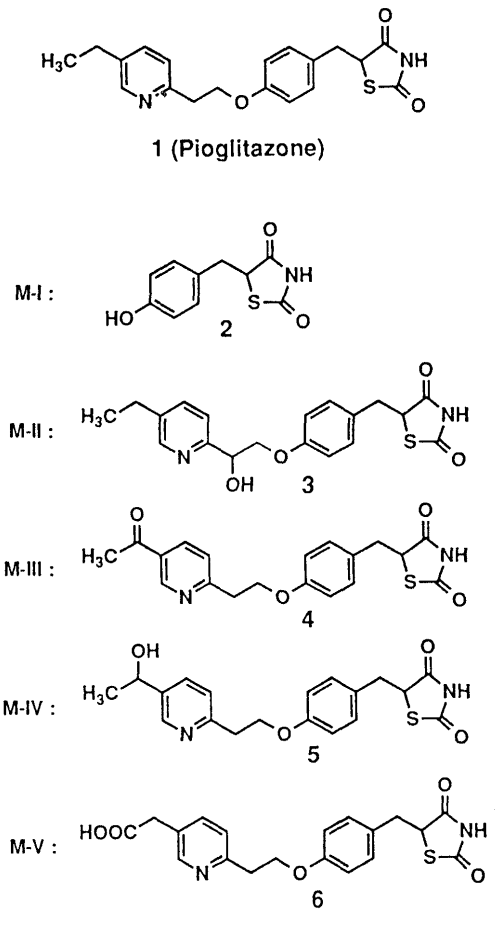

Fig. 1

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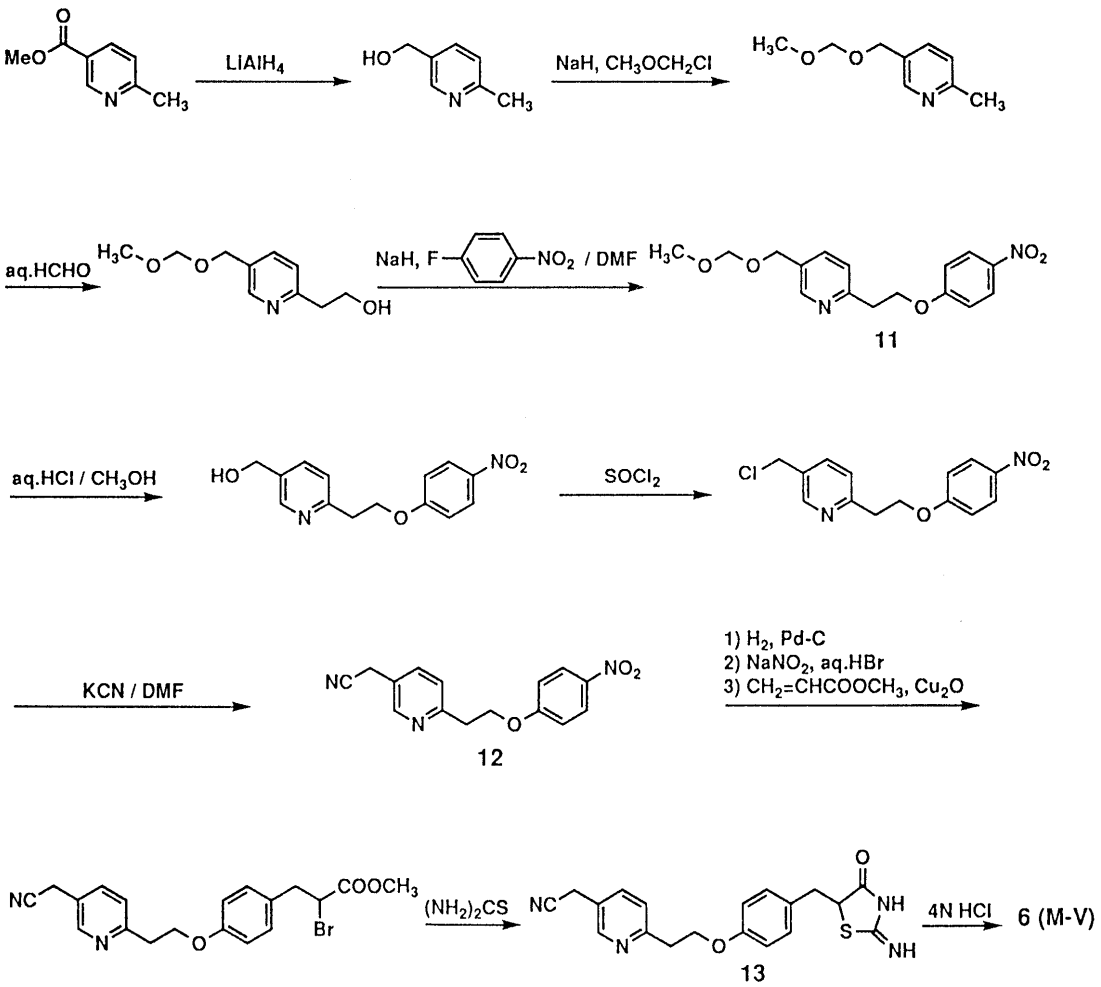

Chart 1

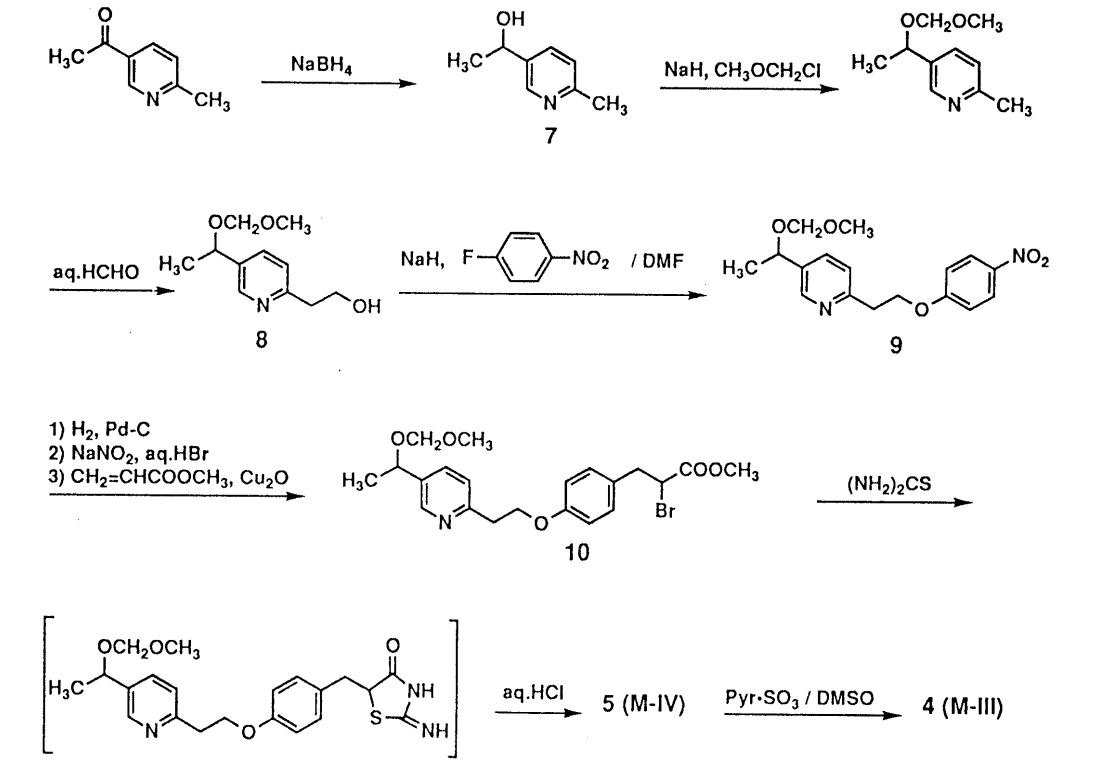

Chart 2

Table 1. Hypoglycemic and Hypolipidemic Activities of the Metabolites of Pioglitazone[a)]

Compound	Hypoglycemic activity ED_{25} (mg/kg/d)	Hypolipidemic activity ED_{25} (mg/kg/d)
3 (M-II)	0.99	0.22
4 (M-III)	1.32	0.47
5 (M-IV)	0.93	0.53
6 (M-V)	>3.0	>3.0
1 (Pioglitazone)	0.54	0.43

a) The phenolic compound **2** (M-I) was inactive in KKA^y mice,[15)] and was not tested in Wistar fatty rats.

(M-V), accompanied with conversion of the cyano moiety to the carboxy moiety (Chart 2).

Biological Results

The metabolites of pioglitazone (**1**, AD-4833) were confirmed to be **2**, **3**, **4**, **5** and **6** by direct comparison [thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC) and mass spectroscopy (MS)] with the authentic compounds.[16)]

The biological activities of the compounds prepared were tested using genetically obese and diabetic Wistar fatty rats[7)] (16-week-old). The rats were divided into experimental groups of five rats each according to their blood glucose levels. The test compounds were given intraperitoneally. The rats were fed the experimental diet and water *ad libitum* for 7 d. Blood samples were taken from the tail vein. Plasma glucose and triglyceride were determined using Encore™ (Baker Instrument Co., Allentown, PA). The maximum decreases in plasma glucose and triglyceride levels were calculated as percentage changes from the control values. Effective dose to reduce plasma glucose and triglyceride levels by 25% (ED_{25}) was determined using data from an experiment in which three different doses (0.3, 1.0 and 3.0 mg/kg/d) were used. ED_{25} (mg/kg/d) was then derived by linear regression analysis of the data.

The hypoglycemic and hypolipidemic activities of the metabolites were shown as ED_{25} values in Table 1. The oxygenated compounds **3**, **4** and **5** were active, although somewhat less so than the parent compound (**1**), while the carboxylic acid derivative (**6**) showed reduced activities at 3 mg/kg. Since these metabolites were abundant in rat[16)] and human plasma,[17)] the results suggest that these metabolites contribute, at least in part, to the pharmacological action of pioglitazone (**1**), as is the case with ciglitazone.[18)]

Experimental

Melting points were taken on a Yanagimoto micro melting point apparatus and were uncorrected. Elemental analyses (C, H and N) were carried out by the Analytical Department of Takeda Chemical Industries, Ltd. ^{1}H-NMR spectra of deuteriochloroform or DMSO-d_6 solutions (internal standard tetramethylsilane (TMS), δ 0) were recorded on a Varian Gemini-200 spectrometer. Infrared spectra were recorded on a Hitachi IR-215 spectrometer. Column chromatography was done with Merck Silica gel 60 (0.063—0.200 mm).

5-(1-Hydroxyethyl)-2-methylpyridine (7) $NaBH_4$ (3.7 g) was added in small portions to an ice-cooled solution of 5-acetyl-2-methylpyridine (26.5 g) in EtOH (150 ml) over a period of 1 h. The mixture was stirred with ice-cooling for 30 min and then AcOH (10 ml) was added. The mixture was concentrated *in vacuo*, and the residue was made alkaline with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The AcOEt extract was dried ($MgSO_4$) and distilled to give **7** as an oil (20.5 g, 76%), bp 110—112 °C/1.0 mmHg. ^{1}H-NMR (δ ppm in $CDCl_3$): 1.50 (3H, d, J=7 Hz), 2.52 (3H, s), 4.90 (1H, d, J=7 Hz), 7.13 (1H, d, J=8 Hz), 7.63 (1H, dd, J=8, 2 Hz), 8.38 (1H, d, J=2 Hz).

5-(1-Methoxymethoxyethyl)-2-methylpyridine An ice-cooled solution of **7** (20.0 g) in *N*,*N*-dimethylformamide (DMF) (120 ml) was treated with NaH (60% in oil, 7.0 g) for 15 min and then chloromethyl methyl ether (14.1 g) was added dropwise. The whole was stirred with ice-cooling for 30 min, poured into H_2O and extracted with AcOEt. The AcOEt extract was dried ($MgSO_4$) and distilled to give the title compound as an oil (21.5 g, 81%), bp 78—80 °C/0.8 mmHg. ^{1}H-NMR (δ ppm in $CDCl_3$): 1.48 (3H, d, J=7 Hz), 2.55 (3H, s), 3.36 (3H, s), 4.53 (1H, d, J=7 Hz), 4.60 (1H, d, J=7 Hz), 4.76 (1H, q, J=7 Hz), 7.14 (1H, d, J=8 Hz), 7.57 (1H, dd, J=8, 2 Hz), 8.45 (1H, d, J=2 Hz).

2-[5-(1-Methoxymethoxyethyl)-2-pyridyl]ethanol (8) A mixture of 5-(1-methoxymethoxyethyl)-2-methylpyridine (21.0 g) and aqueous HCHO (37%, 14.1 g) was heated at 150—160 °C in a sealed tube for 8 h and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (300 g) with $CHCl_3$–MeOH (25 : 1, v/v) to give **8** as an oil (7.8 g, 32%). ^{1}H-NMR (δ ppm in $CDCl_3$): 1.49 (3H, d, J=7 Hz), 3.01 (2H, t, J=6 Hz), 3.36 (3H, s), 4.03 (2H, t, J=6 Hz), 4.53 (1H, d, J=7 Hz), 4.61 (1H, d, J=7 Hz), 4.77 (1H, q, J=7 Hz), 7.15 (1H, d, J=8 Hz), 7.62 (1H, dd, J=8, 2 Hz), 8.46 (1H, d, J=2 Hz).

5-(1-Methoxymethoxyethyl)-2-[2-(4-nitrophenoxy)ethyl]pyridine (9) NaH (60% in oil, 1.6 g) was added in small portions to an ice-cooled mixture of **8** (7.5 g), 4-fluoronitrobenzene (5.0 g) and DMF (50 ml). The whole was stirred with ice-cooling for 1 h, poured into H_2O and extracted with AcOEt. The AcOEt extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (200 g) with $CHCl_3$–MeOH (40 : 1, v/v) to give **9** as an oil (8.4 g, 71%). ^{1}H-NMR (δ ppm in $CDCl_3$): 1.49 (3H, d, J=7 Hz), 3.30 (2H, t, J=6 Hz), 3.36 (3H, s), 4.48 (2H, t, J=6 Hz), 4.52 (1H, d, J=7 Hz), 4.62 (1H, d, J=7 Hz), 4.79 (1H, q, J=7 Hz), 6.97 (2H, d, J=9 Hz), 7.25 (1H, d, J=8 Hz), 7.64 (1H, dd, J=8, 2 Hz), 8.18 (2H, d, J=9 Hz), 8.53 (1H, d, J=2 Hz).

Methyl 2-Bromo-3-[4-[2-[5-(1-methoxymethoxyethyl)-2-pyridyl]-ethoxy]phenyl]propionate (10) A mixture of **9** (8.2 g), 5% Pd–C (50% wet, 0.8 g) and AcOEt (100 ml) was hydrogenated under atmospheric pressure. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residual oil was dissolved in acetone (80 ml)–aqueous HBr (47%, 16.9 g). A solution of $NaNO_2$ (1.9 g) in H_2O (5 ml) was added dropwise to the mixture at 0—5 °C. The whole was stirred at 5 °C and then methyl acrylate (12.7 g) was added. The temperature was raised to 37 °C, and Cu_2O (0.3 g) was added in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated *in vacuo*. The residue was made alkaline with concentrated NH_4OH and extracted with AcOEt. The AcOEt extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (150 g) with Et_2O–hexane–Et_3N (25 : 25 : 1, v/v) to give **10** as an oil (5.6 g, 50%). ^{1}H-NMR (δ ppm in $CDCl_3$): 1.48 (3H, d, J=6 Hz), 3.1—3.4 (2H, m), 3.24 (2H, t, J=6 Hz), 3.36 (3H, s), 3.71 (3H, s), 4.33 (2H, t, J=6 Hz), 4.53 (1H, d, J=7 Hz), 4.61 (1H, d, J=7 Hz), 4.5—4.7 (1H, m), 4.77 (1H, q, J=6 Hz), 6.83 (2H, d, J=9 Hz), 7.09 (2H, d, J=9 Hz), 7.24 (1H, d, J=8 Hz), 7.61 (1H, dd, J=8, 2 Hz), 8.50 (1H, d, J=2 Hz).

5-[4-[2-[5-(1-Hydroxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-thiazolidinedione (5, M-IV) A mixture of **10** (27.0 g), thiourea (4.6 g), NaOAc (4.9 g) and EtOH (250 ml) was stirred under reflux for 4 h and then 2 N HCl (250 ml) was added. The mixture was refluxed for a further 20 h and then concentrated *in vacuo*. The residue was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The AcOEt extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (400 g) with $CHCl_3$–MeOH (40 : 1, v/v) to give **5** as crystals (14.8 g, 66%). Recrystallization from EtOH gave colorless prisms, mp 155—156 °C. ^{1}H-NMR (δ ppm in DMSO-d_6): 1.34 (3H, d, J=6 Hz), 3.04 (1H, dd, J=14, 9 Hz), 3.14 (2H, t, J=7 Hz), 3.30 (1H, dd, J=14, 4 Hz), 4.31 (2H, t, J=6 Hz), 4.7 (1H, m), 4.85 (1H, dd, J=9, 4 Hz), 5.25 (1H, d, J=4 Hz), 6.86 (2H, d, J=9 Hz), 7.13 (2H, d, J=9 Hz), 7.30 (1H, d, J=8 Hz), 7.67 (1H, dd, J=8, 2 Hz), 8.46 (1H, d, J=2 Hz), 11.98 (1H, br d). *Anal.* Calcd for $C_{19}H_{20}N_2O_4S \cdot 1/4C_2H_5OH$: C, 61.00; H, 5.64; N, 7.30. Found: C, 60.87; H, 5.70; N, 7.31.

5-[4-[2-(5-Acetyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (4, M-III) A solution of pyridine–sulfur trioxide complex (44.6 g) in DMSO (50 ml) was added dropwise to an ice-cooled solution of **5**·1/4C_2H_5OH (26.9 g) in CH_2Cl_2 (300 ml)–Et_3N (28.3 g) over a period of 10 min. The mixture was stirred with ice-cooling for 2 h and at room temperature for 1 h, and then H_2O (200 ml) was added. The reaction mixture was concentrated *in vacuo* to a half of the original volume and extracted with AcOEt. The AcOEt extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (700 g) with $CHCl_3$–AcOEt (2 : 1, v/v) to give **4** (10.2 g, 39%) as crystals. Recrystallization from EtOH gave colorless needles, mp 115—116 °C. ^{1}H-NMR (δ ppm in $CDCl_3$): 2.63 (3H, s), 3.11 (1H, dd, J=14, 9 Hz), 3.33 (2H, t, J=6 Hz), 3.42 (1H, dd, J=14, 4 Hz), 4.38 (2H, t, J=6 Hz), 4.49 (1H, dd, J=9, 4 Hz), 6.83 (2H, d, J=9 Hz), 7.12 (2H, d, J=9 Hz), 7.40 (1H, d, J=8 Hz), 8.18 (1H, dd, J=8, 2 Hz), 8.5 (1H, br d), 9.11 (1H, d, J=2 Hz). *Anal.* Calcd for $C_{19}H_{18}N_2O_4S$: C, 61.61; H, 4.90; N, 7.56. Found: C, 61.25; H, 4.88; N, 7.55.

2-Methyl-5-pyridylmethanol A solution of methyl 6-methylnicotinate (45.4 g) in tetrahydrofuran (THF) (50 ml) was added dropwise to a suspension of $LiAlH_4$ (5.7 g) in THF (250 ml) at ambient temperature. The mixture was stirred for 1 h, then H_2O (30 ml) was added dropwise to the mixture. The insoluble solid was filtered off and the filtrate was distilled to give the title compound as an oil (31.0 g, 84%), bp 98—100 °C/0.5 mmHg.

5-Methoxymethoxymethyl-2-methylpyridine Chloromethyl methyl ether (22.1 g) was added dropwise to an ice-cooled mixture of 2-methyl-5-pyridylmethanol (30.8 g), NaH (60% in oil, 11.0 g) and THF (200 ml). The mixture was stirred with ice-cooling for 1 h, poured into H_2O and extracted with AcOEt. The AcOEt extract was dried ($MgSO_4$) and distilled to give the title compound as an oil (31.0 g, 74%), bp 85—87 °C/0.5 mmHg. ^{1}H-NMR (δ ppm in $CDCl_3$): 2.56 (3H, s), 3.41 (3H, s), 4.58 (2H, s), 4.71 (2H, s), 7.15 (1H, d, J=8 Hz), 7.59 (1H, dd, J=8, 2 Hz), 8.48 (1H, d, J=2 Hz).

2-(5-Methoxymethoxymethyl-2-pyridyl)ethanol A mixture of 5-methoxymethoxymethyl-2-methylpyridine (30.5 g) and aqueous HCHO (37%, 22.2 g) was heated at 150 °C in a sealed tube for 8 h. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed on SiO_2 (400 g) with $CHCl_3$–MeOH (20 : 1, v/v) to give the title compound as an oil (11.8 g, 33%). ^{1}H-NMR (δ ppm in $CDCl_3$): 3.02 (2H, t, J=6 Hz), 3.41 (3H, s), 4.02 (2H, t, J=6 Hz), 4.59 (2H, s), 4.71 (2H, s), 7.16 (1H, d, J=8 Hz), 7.64 (1H, dd, J=8, 2 Hz), 8.48 (1H, d, J=2 Hz).

5-Methoxymethoxymethyl-2-[2-(4-nitrophenoxy)ethyl]pyridine (11) NaH (60% in oil, 2.8 g) was added in small portions to an ice-cooled mixture of 2-(5-methoxymethoxymethyl-2-pyridyl)ethanol (11.6 g), 4-fluoronitrobenzene (8.5 g) and DMF (100 ml). The whole was stirred with ice-cooling for 1 h, poured into H_2O and extracted with AcOEt. The AcOEt extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (300 g) with $CHCl_3$–MeOH (40 : 1, v/v) to give **11** as an oil (14.7 g, 79%). ^{1}H-NMR (δ ppm in $CDCl_3$): 3.30 (2H, t, J=6 Hz), 3.41 (3H, s), 4.47 (2H, t, J=6 Hz), 4.60 (2H, s), 4.71 (2H, s), 6.94 (2H, d, J=9 Hz), 7.26 (1H, d, J=8 Hz), 7.66 (1H, dd, J=8, 2 Hz), 8.17 (2H, d, J=9 Hz), 8.54 (1H, d, J=2 Hz).

5-Hydroxymethyl-2-[2-(4-nitrophenoxy)ethyl]pyridine A mixture of **11** (14.5 g), 2 N HCl (50 ml) and MeOH (50 ml) was stirred under reflux for 2 h and concentrated *in vacuo*. The residue was made alkaline with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The AcOEt extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as crystals (9.7 g, 88%). Recrystallization from AcOEt gave colorless prisms, mp 103—104 °C. ^{1}H-NMR (δ ppm in $CDCl_3$): 3.30 (2H, t, J=6 Hz), 4.50 (2H, t, J=6 Hz), 4.72 (2H, s), 6.95 (2H, d, J=9 Hz), 7.25 (1H, d, J=8 Hz), 7.68 (1H, dd, J=8, 2 Hz), 8.16 (2H, d, J=9 Hz), 8.53 (1H, d, J=2 Hz). *Anal.* Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.01; H, 5.14; N, 10.13.

5-Chloromethyl-2-[2-(4-nitrophenoxy)ethyl]pyridine $SOCl_2$ (7.0 g) was added to a mixture of 5-hydroxymethyl-2-[2-(4-nitrophenoxy)-ethyl]pyridine (9.4 g) and $CHCl_3$ (100 ml). The mixture was stirred under reflux for 30 min, cooled, and successively washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as crystals (9.7 g, 85%). Recrystallization from AcOEt–hexane gave colorless needles, mp 77—78 °C. ^{1}H-NMR (δ ppm in $CDCl_3$): 3.31 (2H, t, J=6 Hz), 4.48 (2H, t, J=6 Hz), 4.59 (2H, s), 6.95 (2H, d, J=9 Hz), 7.27 (1H, d, J=8 Hz), 7.70 (1H, dd, J=8, 2 Hz), 8.18 (2H, d, J=9 Hz), 8.56 (1H, d, J=2 Hz). *Anal.* Calcd for $C_{14}H_{13}ClN_2O_3$: C, 57.44; H, 4.48; N, 9.57. Found: C, 57.07; H, 4.42; N, 9.46.

5-Cyanomethyl-2-[2-(4-nitrophenoxy)ethyl]pyridine (12) A mixture of 5-chloromethyl-2-[2-(4-nitrophenoxy)ethyl]pyridine (9.5 g), powdered KCN (3.2 g) and DMF (100 ml) was stirred at 60 °C for 2 h, poured into H_2O and extracted with AcOEt. The AcOEt extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give **12** as crystals (9.0 g, 98%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 94—95 °C. ^{1}H-NMR (δ ppm in $CDCl_3$): 3.31 (2H, t, J=6 Hz), 3.76 (2H, s), 4.48 (2H, t, J=6 Hz), 6.95 (2H, d, J=9 Hz), 7.31 (1H, d, J=8 Hz), 7.64 (1H, dd, J=8, 2 Hz), 8.18 (2H, d, J=9 Hz), 8.52 (1H, d, J=2 Hz). *Anal.* Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.19; H, 4.63; N, 14.41.

Methyl 2-Bromo-3-[4-[2-(5-cyanomethyl-2-pyridyl)ethoxy]phenyl]-propionate A mixture of **12** (8.8 g), 5% Pd–C (50% wet, 1.0 g) and AcOEt (100 ml) was hydrogenated at atmospheric pressure. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residual oil was dissolved in acetone (80 ml)–aqueous HBr (47%, 21.4 g). A solution of $NaNO_2$ (2.4 g) in H_2O (5 ml) was added dropwise to the mixture at 0—5 °C. The whole was stirred at 5 °C and methyl acrylate (16.1 g) was added. The temperature was raised to 37 °C, and Cu_2O (0.3 g) was added in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated *in vacuo*. The residue was made alkaline with concentrated NH_4OH and extracted with AcOEt. The AcOEt extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (150 g) with $CHCl_3$–AcOEt–Et_3N (25 : 25 : 1, v/v) to give the title compound as an oil (7.3 g, 58%). ^{1}H-NMR (δ ppm in $CDCl_3$): 3.1—3.4 (2H, m), 3.26 (2H, t, J=6 Hz), 3.71 (2H, s), 3.74 (3H, s), 4.3—4.4 (1H, m), 4.33 (2H, t, J=6 Hz), 6.76 (2H, d, J=9 Hz), 7.2—7.4 (3H, m), 7.65 (1H, dd, J=8, 2 Hz), 8.50 (1H, d, J=2 Hz).

5-[4-[2-(5-Cyanomethyl-2-pyridyl)ethoxy]benzyl]-2-imino-4-thiazolidinone (13) A mixture of methyl 2-bromo-3-[4-[2-(5-cyanomethyl-2-pyridyl)ethoxy]phenyl]propionate (7.2 g), thiourea (1.2 g), NaOAc (1.3 g) and EtOH (80 ml) was stirred under reflux for 5 h and concentrated *in vacuo*. The residue was diluted with saturated aqueous $NaHCO_3$ (100 ml)–Et_2O (50 ml). The whole was stirred for 15 min and the crystals were collected by filtration to give **13** (2.5 g, 38%). Recrystallization from $CHCl_3$–MeOH gave colorless prisms, mp 211—212 °C. ^{1}H-NMR (δ ppm in DMSO-d_6): 2.83 (1H, dd, J=15, 8 Hz), 3.17 (2H, t, J=7 Hz), 3.28 (1H, dd, J=15, 4 Hz), 4.05 (2H, s), 4.35 (2H, t, J=7 Hz), 4.52 (1H, dd, J=8, 4 Hz), 6.83 (2H, d, J=9 Hz), 7.12 (2H, d, J=9 Hz), 7.40 (1H, d, J=8 Hz), 7.73 (1H, dd, J=8, 2 Hz), 8.49 (1H, d, J=2 Hz), 8.67 (1H, br), 8.88 (1H, br). *Anal.* Calcd for $C_{19}H_{18}N_4O_2S$: C, 62.28; H, 4.95; N, 15.29. Found: C, 62.21; H, 4.89; N, 15.15.

5-[4-[2-(5-Carboxymethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (6, M-V) A mixture of **13** (2.3 g) and 4 N HCl (100 ml) was refluxed for 24 h and concentrated *in vacuo*. The crystalline residue was made alkaline with saturated aqueous $NaHCO_3$ and the resultant solution was acidified with AcOH to give a solid. This solid was collected by filtration and dissolved in AcOEt (200 ml)–MeOH (20 ml). The solution was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give **6** as crystals (1.9 g, 79%). Recrystallization from EtOH gave colorless prisms, mp 144—145 °C. ^{1}H-NMR (δ ppm in DMSO-d_6): 3.04 (1H, dd, J=14, 9 Hz), 3.18 (2H, t, J=7 Hz), 3.29 (1H, dd, J=14, 4 Hz), 4.31 (2H, t, J=7 Hz), 4.85 (1H, dd, J=9, 4 Hz), 6.86 (2H, d, J=9 Hz), 7.13 (2H, d, J=9Hz), 7.30 (1H, d, J=8 Hz), 7.61 (1H, dd, J=8, 2 Hz), 8.38 (1H, d, J=2 Hz). *Anal.* Calcd for $C_{19}H_{18}N_2O_5S$: C, 59.06; H, 4.70; N, 7.25. Found: C, 58.89; H, 4.69; N, 7.08.

References and Notes

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