Synthesis of 2-Substituted 4-Pyridylpropionates. Part 2.[1] Alkylation Approach

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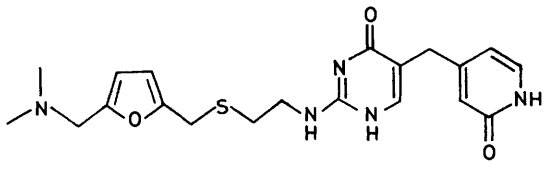
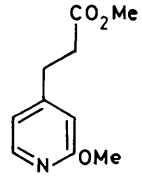
A synthesis of methyl 3-(2-methoxy-4-pyridyl)propionate (**2**), a key intermediate in the synthesis of the potent long-acting histamine H_2-receptor antagonist SK&F 93574 (**1**), is described. The key step in the synthesis of compound (**1**) involves alkylation of 2-methoxy-4-methylpyridine (**5**) with sodium chloroacetate in the presence of sodamide. The scope and limitations of the alkylation is investigated using a variety of electrophiles. The application of this reaction to other 2-substituted 4-methylpyridines is also discussed.

Among the second generation histamine H_2-receptor antagonists discovered with high potency and long duration of action is SK&F 93574 (**1**).[2] The key intermediate required for the construction of the pyridylmethyl-substituted isocytosine moiety is methyl 3-(2-methoxy-4-pyridyl)propionate (**2**).[1,3] In the preceding paper,[1] a synthesis of compound (**2**) was described *via* a Claisen ester condensation on a 2-substituted methyl isonicotinate. Although the chemistry described[1] was successful on the laboratory scale, we required large quantities of the pyridylpropionate (**2**), and therefore an alternative and more efficient method of preparation of this intermediate was required.



(**1**)

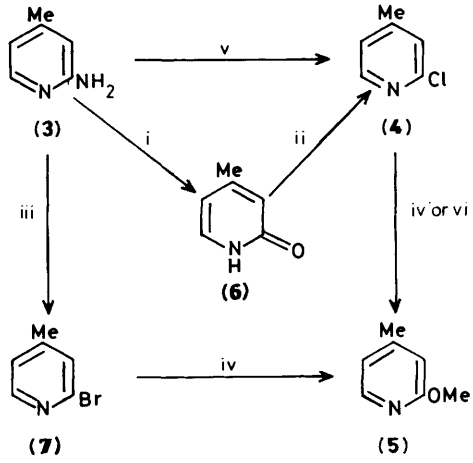


(**2**)

The alkylation of 2- and 4-methylpyridines *via* the corresponding methylpyridyl anion is a well known reaction,[4–7] and to apply this approach to the synthesis of compound (**2**) we required 4-methylpyridine to have a masked hydroxy function at the 2-position. Of the few 2,4-disubstituted pyridines commercially available, 2-amino-4-methylpyridine (**3**) was chosen as a starting material for the preparation of substrates for alkylation.

Results and Discussion

(i) *Methylpyridines* (**4**) *and* (**5**).—The synthesis of the required intermediates (**4**) and (**5**) was carried out as shown in Scheme 1. Diazotisation of 2-amino-4-methylpyridine (**3**) in aqueous



Scheme 1. *Reagents and conditions:* i, dil. H_2SO_4–$NaNO_2$, 59%; ii, $POCl_3$, 90 °C, 74%; iii, 48% HBr–Br_2–$NaNO_2$, 81%; iv, NaOMe–DMF, 80%; v, conc. HCl–HCl(g)–$NaNO_2$, 54%; vi, 30% NaOMe–MeOH, reflux, 90%

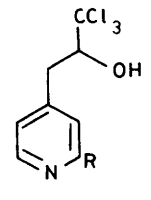
sulphuric acid gave 4-methyl-2(1*H*)-pyridone[8] (**6**) in reasonable to good yield in the laboratory; however, on scale-up isolation of the water-soluble pyridone (**6**) became a problem leading to variable yields. This problem was partially overcome by extracting compound (**6**) from the aqueous reaction mixture at pH 6.5—7.0 with ethyl acetate at 60 °C; however, this procedure resulted in the carry over of sodium sulphate generated on basification of the reaction mixture. Treatment of pyridone (**6**) with neat phosphorus oxychloride at 90 °C for 2 h gave the desired 2-chloro-4-methylpyridine (**4**) in good yield.

In view of the problems encountered with the isolation of pyridone (**6**), direct conversion of aminomethylpyridine (**3**) into a 2-halo-4-methylpyridine appeared attractive. Reaction of (**3**) under standard Sandmeyer conditions would give rise to substantial amounts of (**6**) owing to the high reactivity of 2-pyridyl diazonium salts with water. The aminomethylpyridine (**3**) has been converted into 2-bromo-4-methylpyridine (**7**) by the Craig reaction.[9,10] Although high yields of the methylpyridine (**7**) were obtained, the reaction mixture became very thick on addition of bromine to the substrate in 48% hydrobromic acid. Despite efforts to keep the mixture mobile during the course of the reaction, stirring was difficult. This behaviour rendered the reaction unsuitable for large-scale preparations of the pyridine (**7**). An adaptation of the Craig reaction was investigated, by adding aqueous sodium nitrite to the solution of substrate (**3**) in concentrated hydrochloric acid.

Low yields of the desired 2-chloro-4-methylpyridine (**4**) were obtained, and the major by-product (**6**) was produced by competitive reaction of the diazonium salt with water. Reasonable yields of compound (**4**) were obtained by carrying out the reaction in concentrated hydrochloric acid saturated with hydrogen chloride gas at 0—5 °C. In addition to providing (**4**) directly from (**3**), the yield obtained in this reaction (54%) compared well with that of the two-step procedure (44%) *via* the pyridone (**6**).

Conversion of compounds (**4**) and (**7**) into 2-methoxy-4-methylpyridine (**5**) was initially carried out using sodium methoxide in dimethylformamide (DMF). As DMF decomposes in the presence of bases,[3] and also for safety reasons, an alternative procedure was required. It was found that a temperature of >80 °C was required before methoxide displacement occurred, and use of commercially available 30% sodium methoxide in methanol under reflux was found to give good yields of compound (**5**).

(ii) *Methyl* 3-(2-*Methoxy*-4-*pyridyl*)*propionate* (**2**).—Having obtained the intermediates (**4**) and (**5**), a series of alkylations were investigated. Condensation of methylpyridines with chloral is a known reaction,[11,12] and repetition of this reaction on the intermediates (**4**) and (**5**) would furnish the useful products (**8**) and (**9**). All attempts to condense chloral with or without added base led only to the isolation of the starting pyridine (**4**) or (**5**).

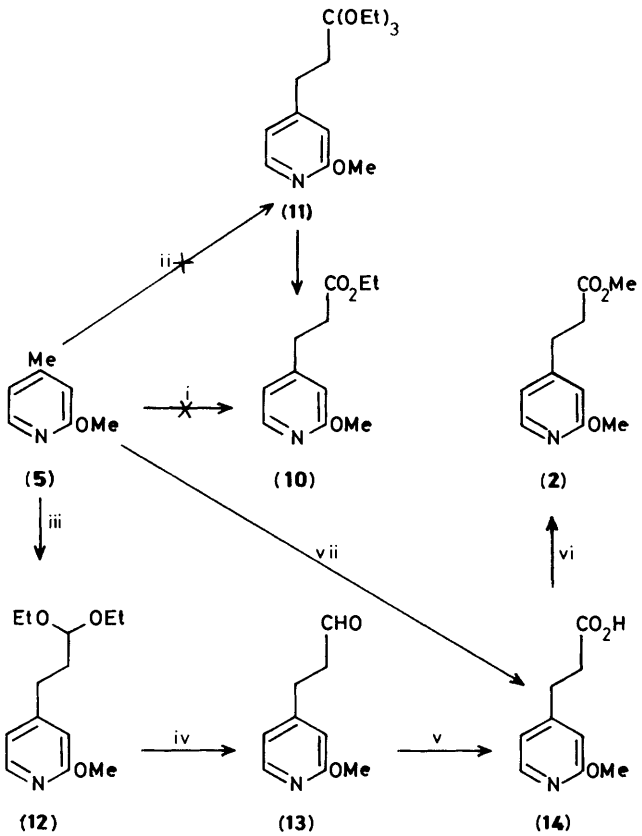


R
(**8**) Cl
(**9**) OMe

Since we have already investigated the alkylation of methylpyridines using sodamide in liquid ammonia in the presence of an electrophile,[7] a series of alkylations using compound (**5**) as substrate were investigated (Scheme 2).

Generation of the orange methylpyridyl anion of (**5**) was facile on the addition of sodamide to refluxing anhydrous ammonia. Attempts to prepare the ester (**10**) by treatment of this anion with ethyl bromoacetate or ethyl chloroacetate led to the isolation of starting materials only. The methylene protons of the ethyl haloacetates must therefore be sufficiently acidic to exchange with methylpyridyl anion in preference to halide displacement. Treatment of the anion of (**5**) with ethyl orthobromoacetate[13] gave on work-up a mixture of (**5**), the desired orthoester (**11**), and ethyl orthobromoacetate in the ratio of 2:1:2 by n.m.r. analysis. Attempts to alter the selectivity of this reaction failed, which indicated that competition between proton abstraction from the methylene group of ethyl orthobromoacetate and bromine displacement occurs. Treatment of the anion of (**5**) with bromoacetaldehyde diethyl acetal, however, gave high isolated yields of (**12**). It was found to be essential to use 1 equiv. of sodamide, since greater quantities gave rise to significant quantities of the corresponding bis-alkylated pyridine (**15**). This indicates that the formation of the anion of (**12**) is facile and reaction is not subject to substantial steric hindrance.

Conversion of the acetal (**12**) into the aldehyde (**13**) using



Scheme 2. *Reagents and conditions:* i, $NaNH_2$–liq. NH_3–$BrCH_2CO_2Et$; ii, $NaNH_2$–liq. NH_3–$BrCH_2C(OEt)_3$; iii, $NaNH_2$–liq. NH_3–$BrCH_2CH(OEt)_2$, 94%; iv, water–HOAc, reflux, 74%; v, $KMnO_4$–Me_2CO–Aliquot 336, 72%; vi, MeOH, conc. H_2SO_4, reflux, 80%; vii, $NaNH_2$–liq. NH_3–$ClCH_2CO_2Na$, 61%

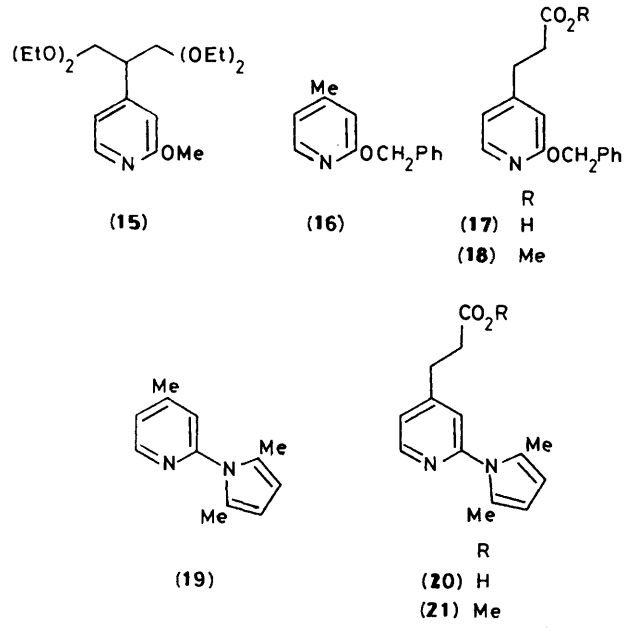
aqueous acetic acid at 100—110 °C occurred readily. Direct conversion of aldehydes into esters has been reported[14,15] and attempts to carry out these procedures gave rise to multiple products or intractable tars. Oxidation of aldehydes to acids is not a trivial transformation for large-scale operations. Treatment of (**13**) with Jones reagent in acetone or glacial acetic acid gave rise to voluminous precipitates and thick emulsions on work-up, or very low yields of the desired acid. In addition, use of chromium reagents on a large scale is undesirable owing to toxicity of the reagents and difficulty in the treatment of effluent generated. Calcium hypochlorite has been used for the oxidation of aldehydes to acids;[16] however, when applied to the aldehyde (**13**), only intractable tars were obtained. Oxidation using aqueous potassium permanganate at 70—80 °C resulted in smooth conversion into the acid (**14**) by t.l.c. analysis, but isolation of the product from the dilute aqueous reaction mixture was difficult. Use of potassium permanganate in wet acetone using Aliquat 336 as a solid liquid phase-transfer catalyst also gave the acid (**14**). Although reasonable yields of the desired product were obtained, isolation problems were still experienced which led to variable yields. Conversion of the acid (**14**) into the required ester (**2**) was accomplished in good yield by refluxing in methanol with *ca.* 7% concentrated sulphuric acid.

The conversion of compound (**5**) *via* the acetal (**12**) into the ester (**2**) is long, and only gives fair overall yields. Direct conversion of (**5**) into the acid (**14**) would be more desirable, but the acidity of methylene protons in haloacetates as described earlier is a problem. It was considered that the methylene

protons of sodium chloroacetate would be sufficiently less acidic, due to the proximity of the carboxylate anion, to enable halide displacement to occur preferentially. Thus reaction of the anion of (**5**), generated by sodamide in refluxing anhydrous ammonia, with sodium chloroacetate gave reasonable yields (~ 55%) of the acid (**14**). The reaction mixture is heterogeneous, which could lead to variable yields. The yield of the acid (**14**) obtained was found to be insensitive to the nature of the halide displaced (*i.e.* Cl, Br), counter ion of the acid, and presence of co-solvents such as tetrahydrofuran or dioxane. The procedure described above has been scaled up to 33 mol, and forms the basis of an efficient route to the ester (**2**).[17]

(iii) *Alternative 2-Substituents.*—Other masked hydroxy groups are available, such as benzyl ether and 2,5-dimethylpyrrole[18] moieties. Thus the alkylation of methylpyridines (**16**) and (**19**) with sodium chloroacetate was investigated. Treatment of methylpyridine (**4**) with the sodium salt of benzyl alcohol gave the corresponding benzyl ether (**16**), which forms the methylpyridyl anion rapidly on treatment with sodamide in liquid ammonia. Treatment of this anion with sodium chloroacetate gave the acid (**17**) in about 60% yield. Treatment of acid (**17**) with refluxing methanol containing sulphuric acid gave the corresponding ester (**18**) in high yield. The advantage of the benzyl ether is that removal is mild under hydrogenolysis conditions to give the corresponding 2(1*H*)-pyridone.

Alkylation of 2-amino-6-methylpyridine with the amino group protected as the 2,5-dimethylpyrrole moiety has been described.[18] Thus, conversion of the amine (**3**) into the protected amine (**19**) was carried out by the method of Meakins.[18] The anion of (**19**) generated with sodamide in liquid ammonia reacted smoothly with sodium chloroacetate to give the acid (**20**) as an amorphous solid. Attempts to recrystallise the acid (**20**) failed. Crude (**20**) was esterified as previously described to give compound (**21**) as an air-sensitive oil.



In conclusion alkylation of 2-substituted 4-methylpyridyl anions with sodium chloroacetate forms the basis of three routes into useful intermediates for the preparation of SK&F 93574 (**1**). Yields obtained in the alkylation appear to be relatively insensitive to the nature of the 2-substituent, the nature of the halide displaced, and the counter ion of the electrophile.

Experimental

Materials and Equipment.—M.p.s were determined on a Buchi 510 melting point apparatus and are uncorrected. Unless otherwise stated i.r. spectra were recorded of Nujol mulls on a Perkin-Elmer 781 instrument, n.m.r. spectra of deuteriochloroform solutions with tetramethylsilane as internal standard on a Varian EM360 instrument. Mass spectra were recorded on a VG7070F spectrometer. 2-Amino-4-methylpyridine (**3**) was obtained from Reilly Tar and Chemical Corporation. Light petroleum refers to the fraction boiling at 60—80 °C.

4-*Methyl*-2(1H)-*pyridone* (**6**).—Water (1.2 l) was placed in a 5 l flange flask and concentrated sulphuric acid (289 g) was added with cooling and stirring. The aqueous sulphuric acid was then cooled below 0 °C, and 2-amino-4-methylpyridine (150.6 g, 1.39 mol) was added. The resultant solution was treated with a solution of sodium nitrite (103.1 g, 1.49 mol) in water (200 ml) at such a rate that the internal temperature remained below 5 °C. After the addition was complete, the reaction mixture was stirred at 0—5 °C for 45 min and then heated to 95 °C for 15 min. The reaction mixture was cooled, basified with 50% w/w aqueous sodium hydroxide to pH 6.5—7.0, and heated to 60 °C. The hot reaction mixture was extracted with ethyl acetate (4 × 500 ml + 1 × 400 ml) and the combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was recrystallised from ethyl acetate (750 ml)–light petroleum (500 ml) to give 4-methyl-2(1*H*)-pyridone (**6**) (89.5 g, 59%) as a white crystalline solid, m.p. 128 °C (lit.,[8] 130 °C) (Found: C, 66.1; H, 6.8; N, 12.8. Calc. for C_6H_7NO: C, 66.0; H, 6.5; N, 12.8%); $\nu_{max.}$ 3 360 (OH), 3 120 (NH), 1 660 (C=O), 1 612, 1 585, and 1 450 (C=C) cm^{-1}; δ[$(CD_3)_2SO$] 2.10 (3 H, s, py-Me), 6.02 (1 H, dd, *J* 7.0 and 2.0 Hz, py-H), 6.15 (1 H, m, py-H), 7.24 (1 H, d, *J* 7.0 Hz, py-H), and 11.20 (1 H, br s, NH).

2-*Chloro*-4-*methylpyridine* (**4**) *from Compound* (**6**).—Phosphorus oxychloride (200 ml, 2.2 mol) was placed in a 1 l flask fitted with a mechanical stirrer, thermometer, and reflux condenser, and was warmed to 45 °C. 4-Methyl-2(1*H*)-pyridone (**6**) (131 g, 1.2 mol) was cautiously added to the flask, the contents of the flask were heated to 90 °C and stirred at this temperature for 2 h. The reaction mixture was cooled to 30 °C, and cautiously quenched into water (2.5 l) containing 0.880 aqueous ammonia (500 ml), keeping the temperature at 20—35 °C. The quenched reaction mixture was basified to pH 10—10.5 with 0.880 aqueous ammonia and extracted with dichloromethane (4 × 500 ml). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to yield an oil, which was distilled under reduced pressure to give 2-chloro-4-methylpyridine (**4**) (114 g, 74%) as a colourless liquid, b.p. 68—69 °C at 4 mmHg (lit.,[19] 84—85 °C at 17 mmHg) (Found: C, 56.0; H, 4.6; Cl, 28.2; N, 10.8. Calc. for C_6H_6ClN: C, 56.5; H, 4.7; Cl, 27.8; N, 11.0%); $\nu_{max.}$(liq. film) 1 595, 1 560, 1 465 (C=C), and 710 cm^{-1} (C–Cl); δ 2.33 (3 H, s, py-Me), 7.03 (1 H, br d, *J* 5 Hz, py-H), 7.14 (1 H, m, py-H), and 8.23 (1 H, d, *J* 5 Hz, py-H).

2-*Chloro*-4-*methylpyridine* (**4**) *from Compound* (**3**).—A mechanically stirred solution of 2-amino-4-methylpyridine (**3**) (22 g, 0.20 mol) in concentrated hydrochloric acid (176 ml) was cooled to 0—5 °C and saturated carefully with hydrogen chloride gas. The resulting mixture was cooled to 0—5 °C and treated with a solution of sodium nitrite (30 g, 0.43 mol) in water (60 ml) over a period of 6 h. After addition was complete, the reaction mixture was basified with 50% w/v aqueous sodium hydroxide to pH 12 and extracted with dichloromethane (4 × 800 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to leave an oil

which after distillation under reduced pressure gave 2-chloro-4-methylpyridine (**4**) (14.1 g, 54%) as a colourless liquid, b.p. 68—69 °C at 4 mmHg, spectroscopically identical with the material produced from the pyridone (**6**).

2-Bromo-4-methylpyridine (**7**).—2-Amino-4-methylpyridine (**3**) (10.8 g, 0.1 mol) was carefully added to 48% aqueous hydrogen bromide (60 ml) contained in a 250 ml flask fitted with a mechanical stirrer, thermometer, and reflux condenser. The resultant solution was cooled to below 5 °C, and bromine (48 g, 0.3 mol) was slowly added, keeping the internal temperature below 5 °C. At this point the mixture became thick and stopped stirring, thus 48% aqueous hydrogen bromide (20 ml) was added to aid mixing. The thick mixture was stirred for 1 h at 0 °C then treated with a solution of sodium nitrite (17.3 g, 0.25 mol) in water (30 ml) at such a rate that the internal temperature was kept below 5 °C. The resulting brown–black solution was allowed to warm to 10 °C, then basified to pH 12 with 50% w/w aqueous sodium hydroxide, keeping the internal temperature below 30 °C. The resulting yellow solution was extracted with dichloromethane (3 × 100 ml), and the combined organic layers were washed with water (2 × 100 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil was distilled under reduced pressure to give the *title compound* (**7**) (14 g, 81%) as a colourless liquid, b.p. 75 °C at 3.5 mmHg (lit.,[10] 87 °C at 10 mmHg); $\nu_{max.}$(liq. film) 1 595, 1 550, 1 530, 1 460 (C=C), and 695 cm^{-1} (C–Br); δ 2.25 (3 H, s, py-Me), 7.05 (1 H, d, *J* 5 Hz, py-H), 7.39 (1 H, s, py-H), and 8.28 (1 H, d, *J* 5 Hz, py-H).

2-Methoxy-4-methylpyridine (**5**) *from Compound* (**4**) *or* (**7**) *Using Sodium Methoxide in DMF.*—A solution of 2-chloro-4-methylpyridine (**4**) (40 g, 0.31 mmol) in DMF (220 ml) under a blanket of nitrogen was treated with sodium methoxide (52.6 g, 0.97 mol) and the resulting mixture was stirred and heated to 100 °C. After 30 min the reaction mixture was cooled and quenched into water (500 ml), extracted with toluene (4 × 300 ml) and the combined toluene layers were washed with water (4 × 300 ml) and then extracted with 20% aqueous sulphuric acid (3 × 300 ml). The combined acid extracts were basified to pH 10.5 with aqueous 0.880 ammonia and extracted with dichloromethane (4 × 300 ml). The combined dichloromethane layers were dried ($MgSO_4$) and evaporated under reduced pressure go give an oil. Distillation under reduced pressure gave 2-methoxy-4-methylpyridine (**5**) (30.6 g, 79%) as a colourless liquid, b.p. 48—50 °C at 7 mmHg (lit.,[20] 67 °C at 21 mmHg) (Found: C, 68.0; H, 7.6; N, 10.9. Calc. for C_7H_9NO: C, 68.3; H, 7.4; N, 11.4%); $\nu_{max.}$(liq. film) 1 610, 1 560, 1 480, and 1 450 cm^{-1} (C=C); δ 2.28 (3 H, s, py-Me), 3.92 (3 H, s, OMe), 6.55 (1 H, s, py-H), 6.69 (1 H, d, *J* 5 Hz, py-H), and 8.01 (1 H, d, *J* 5 Hz, py-H).

Repetition of the reaction described above with 2-bromo-4-methylpyridine (**7**) (110 g, 0.64 mmol) in DMF (340 ml) and sodium methoxide (108 g, 2.0 mol) gave, after work-up and distillation, 2-methoxy-4-methylpyridine (**5**) (65.0 g, 83%), spectroscopically identical with the material produced previously.

2-Methoxy-4-methylpyridine (**5**) *Using* 30% *Sodium Methoxide in Methanol.*—2-Chloro-4-methylpyridine (**4**) (500 g, 3.9 mol) was added to a solution of sodium methoxide (30% w/v; 1.4 kg, 7.8 mol) and the resulting solution was refluxed overnight. The reaction mixture was cooled, poured into water (1 l), and extracted with dichloromethane (2 × 1 l, 1 × 500 ml). The combined dichloromethane layers were dried ($MgSO_4$) and evaporated to give 2-methoxy-4-methylpyridine (**5**) (437 g, 90%) as a pale yellow oil which was suitable for subsequent reactions without further purification. The product obtained by this procedure was spectroscopically identical with that described earlier.

Alkylation of 2-Methoxy-4-methylpyridine (**5**) *with Bromoacetaldehyde Diethyl Acetal.*—Liquid ammonia (1 l) was placed in a 2 l flask fitted with a mechanical stirrer and solid CO_2–acetone condenser. Sodamide (13.9 g, 0.36 mol) was quickly added, followed by 2-methoxy-4-methylpyridine (**5**) (40.0 g, 0.33 mol). The resulting mixture was stirred for 30 min during which time the characteristic orange colour of the methylpyridyl anion developed. The orange mixture was carefully treated with bromoacetaldehyde diethyl acetal (64.3 g, 0.33 mol). The dark mixture was stirred for 1.5 h and then treated with ammonium chloride (20 g, 0.49 mol). Ammonia was allowed to evaporate, and the residue was dissolved in water (400 ml) and extracted with dichloromethane (3 × 200 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give 3-(2-*methoxy*-4-*pyridyl*)*propionaldehyde diethyl acetal* (**12**) (74.2 g, 94%) as a pale yellow oil which was sufficiently pure for subsequent reactions without further purification; b.p. 106 °C at 0.4 mmHg (Found: C, 64.6; H, 8.6; N, 5.7%; M^+, 239.1533. $C_{13}H_{21}NO_3$ requires C, 65.2; H, 8.8; N, 5.9%; *M*, 239.1521); $\nu_{max.}$(liq. film) 2 970 (C–H), 1 609, 1 556, 1 478, and 1 445 cm^{-1} (C=C); δ 1.21 (6 H, t, *J* 7.0 Hz, 2 × OCH_2Me), 1.79—2.22 (2 H, m, CH_2CH_2), 2.51—2.97 (2 H, m, CH_2CH_2), 3.26—4.0 (4 H, m, 2 × OCH_2Me), 4.0 (3 H, s, OMe), 4.62 [1 H, t, *J* 6.0 Hz, $CH(OEt)_2$], 6.83 (1 H, apparent s, py-H), 6.93 (1 H, dd, *J* 5.0 and 1.5 Hz, py-H), and 8.34 (1 H, d, *J* 5.0 Hz, py-H); *m/z* 239 (M^+, 10%), 194 (10, *M* − OEt), 164 (15), 148 (61), 123 (85), 103 (87), 75 (77), and 47 (100).

3-(2-*Methoxy*-4-*pyridyl*)*propionaldehyde* (**13**).—The acetal (**12**) (405 g, 1.7 mol) was added to glacial acetic acid (300 ml) and water (153 ml) and the resulting solution was heated under reflux with stirring. After 4 h the mixture was cooled, poured into water (1 l), and neutralised to pH 6.5 with saturated aqueous sodium hydrogen carbonate. The resulting mixture was extracted with dichloromethane (1 × 1.5 l + 1 × 1 l) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil, which was distilled under reduced pressure to give the *title compound* (**13**) (208 g, 74%) as a colourless oil which was found to partially oxidise to the corresponding acid on contact with air; b.p. 92—94 °C at 0.4 mmHg (Found: C, 64.7; H, 6.9; N, 8.2%; M^+, 165.0795. $C_9H_{11}NO_2$ requires C, 65.4; H, 6.7; N, 8.5%; *M*, 165.0790); $\nu_{max.}$(liq. film) 2 940, 2 280, 2 720 (C–H), 1 725 (C=O), 1 610, 1 560, 1 480, and 1 460 cm^{-1} (C=C); δ 2.82 (4 H, s, CH_2CH_2), 3.85 (3 H, s, OMe), 6.60 (1 H, s, py-H), 6.75 (1 H, d, *J* 5.0 Hz, py-H), 8.01 (1 H, d, *J* 5.0 Hz, py-H), and 9.90 (1 H, s, CHO).

Oxidation of the Aldehyde (**13**).—A solution of the aldehyde (**13**) (68.6 g, 0.42 mol) in acetone (247 ml) was treated with Aliquat 336 (1.3 g). Potassium permanganate (65.6 g, 0.42 mol) was carefully added with stirring and cooling as necessary to keep the internal temperature at 25 °C. The reaction mixture was mechanically stirred for 1.5 h at 25 °C, then water (250 ml) containing sodium metabisulphite (5 g) and potassium hydroxide (10 g) was added to the reaction mixture (pH 8). The resultant slurry was heated to 50 °C and then filtered hot. The filter cake was washed with hot acetone (100 ml), the combined filtrates were reduced in volume under reduced pressure to remove acetone, and acidified to pH 4.5 with concentrated hydrochloric acid. The mixture was cooled, filtered, and the filter cake washed with cold water and then dried at 50 °C *in vacuo* to give 3-(2-*methoxy*-4-*pyridyl*)*propionic acid* (**14**) (41.1 g, 55%) as a white crystalline solid. Further extraction of the manganese dioxide solids yielded more acid (**14**) (12.8 g), total yield 72%, m.p. 115—115.5 °C (methanol) (Found: C, 59.7; H, 6.4; N, 7.8. $C_9H_{11}NO_3$ requires C, 59.7; H, 6.1; N, 7.7%); $\nu_{max.}$ 3 360—2 200 (OH), 1 720 (C=O), 1 615, 1 550, 1 450, and 1 400 cm^{-1} (C=C); δ[$(CD_3)_2SO$] 2.45—3.15 (4 H, m, CH_2CH_2), 3.93

(3 H, s, OMe), 6.75 (1 H, apparent s, py-H), 6.95 (1 H, dd, *J* 5.0 and 1.5 Hz, py-H), 8.17 (1 H, d, *J* 5.0 Hz, py-H), and 9.35 (1 H, br s, CO_2H).

Methyl 3-(2-Methoxy-4-pyridyl)propionate (**2**).—A solution of the acid (**14**) (54.3 g, 0.3 mol) in methanol (360 ml) was treated with concentrated sulphuric acid (27 ml) and heated under reflux for 4.5 h. The reaction mixture was cooled and concentrated *in vacuo* to a total volume of *ca.* 100 ml. The resulting solution was quenched into water (400 ml), basified to pH 10 with 0.880 aqueous ammonia, and extracted with dichloromethane (3 × 200 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to give an orange oil (56.2 g), which was distilled under reduced pressure to give the *title compound* (**2**) (46.2 g, 80%) as a colourless oil, b.p. 96—104 °C at 0.01 mmHg (Found: C, 61.6; H, 6.8; N, 7.1. $C_{10}H_{13}NO_3$ requires C, 61.5; H, 6.7; N, 7.2%); $\nu_{max.}$(liq. film) 1 740 (C=O), 1 615, 1 560, 1 485, and 1 450 cm^{-1} (C=C); δ 2.40—3.20 (4 H, m, CH_2CH_2), 3.69 (3 H, s, CO_2Me), 3.93 (3 H, s, OMe), 6.57 (1 H, apparent s, py-H), 6.73 (1 H, dd, *J* 5.0 and 1.5 Hz, py-H), and 8.07 (1 H, d, *J* 5.0 Hz, py-H).

Alkylation of 2-Methoxy-4-methylpyridine (**5**) *with Sodium Chloroacetate.*—Liquid ammonia (1.6 l) was placed in a 3 l flask fitted with a mechanical stirrer and solid CO_2–acetone condenser. Sodamide (23 g, 0.59 mol) was quickly added, followed by 2-methoxy-4-methylpyridine (**5**) (50 g, 0.40 mol). The resulting mixture was stirred for 30 min. The dark orange mixture was carefully treated with sodium chloroacetate (47.0 g, 0.40 mol). After 1.5 h a second portion of sodium chloroacetate (47.4 g, 0.40 mol) was added. After a total reaction time of 3.5 h, the reaction mixture was treated with ammonium chloride (74.4 g, 1.4 mol). Ammonia was allowed to evaporate and the solid residue was treated with water (720 ml) and extracted with dichloromethane (1 × 500 ml + 2 × 125 ml). The aqueous layer was acidified to pH 1 with concentrated hydrochloric acid and then extracted with ethyl acetate (3 × 250 ml). The aqueous layer was basified to pH 4.5 with 40% w/v aqueous sodium hydroxide, then cooled to 0—5 °C, and stirred at this temperature for 2 h. The mixture was filtered under reduced pressure and the filter cake was washed with water (30 ml), and dried at 50 °C *in vacuo* to give 3-(2-methoxy-4-pyridyl)propionic acid (**14**) (44.0 g, 61%) as a white crystalline solid, m.p. 114—115 °C, spectroscopically identical with the material prepared by oxidation of the aldehyde (**13**) described earlier.

2-Benzyloxy-4-methylpyridine (**16**).—DMF (200 ml) was placed in a 500 ml flask fitted with a thermometer, calcium chloride drying tube, and mechanical stirrer, and cooled to 0 °C. Sodium hydride (16.8 g of a 57% suspension in oil, 0.40 mol) was slowly added to the cooled DMF, followed by benzyl alcohol (44.0 g, 0.41 mol) at such a rate that the internal temperature was kept below 10 °C. After addition of benzyl alcohol was complete, the reaction mixture was allowed to warm to room temperature, and stirred for 1 h. The resulting mixture was then treated with 2-chloro-4-methylpyridine (**4**) (25.5 g, 0.20 mol) and the mixture was warmed to 75—80 °C. After 1 h the reaction mixture was cooled to ambient and poured into water (400 ml). The quenched mixture was extracted with toluene (3 × 200 ml) and the combined toluene layers were washed with water (3 × 150 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give a yellow-brown oil, which was distilled under reduced pressure to give the title compound (**16**) (33.4 g, 84%) as a colourless oil, b.p. 124—130 °C at 0.15 mmHg (lit.,[9] 142—145 °C at 5 mmHg) (Found: C, 78.0; H, 6.8; N, 6.6. Calc. for $C_{13}H_{13}NO$: C, 78.4; H, 6.6; N, 7.0%); $\nu_{max.}$(liq. film) 3 060, 3 020, 2 930 (C–H), 1 610, 1 560, 1 480, 1 450, and 1 410 cm^{-1} (C=C); δ 2.21 (3 H, s, py-Me), 5.42 (2 H, s, $ArCH_2$), 6.65 (1 H, apparent s, py-H), 6.68 (1 H, dd, *J* 5.0 and 1.5 Hz, py-H), 7.19—7.62 (5 H, m, ArH), and 8.09 (1 H, d, *J* 5.0 Hz, py-H).

Alkylation of 2-Benzyloxy-4-methylpyridine (**16**) *with Sodium Chloroacetate.*—Liquid ammonia (2 l) was placed in a 5 l flask fitted with a mechanical stirrer and solid CO_2–acetone condenser. Sodamide (19.6 g, 0.40 mol) was quickly added, followed by 2-benzyloxy-4-methylpyridine (**16**) (78.6 g, 0.40 mol), and the resulting mixture was stirred for 30 min. The resulting orange mixture was treated cautiously with sodium chloroacetate (47.0 g, 0.40 mol). After stirring for 2.5 h, the reaction mixture was treated with ammonium chloride (21.4 g, 0.40 mol). Ammonia was allowed to evaporate and the residue was dissolved in water (1.3 l) and extracted with dichloromethane (600 ml). The aqueous layer was filtered and acidified to pH 4.5 with concentrated hydrochloric acid, then cooled to 0 °C, and stirred at this temperature for 1.5 h. The resultant mixture was filtered and the filter cake was washed with cold water (30 ml) and dried at 80 °C *in vacuo* to give 3-(2-*benzyloxy*-4-*pyridyl*)*propionic acid* (**17**) (71.0 g, 70%) as a white crystalline solid, m.p. 120—121 °C (MeOH) (Found: C, 69.9; H, 5.9; N, 5.4. $C_{15}H_{15}NO_3$ requires C, 70.0; H, 5.9; N, 5.4%); $\nu_{max.}$ 3 100—2 400 (OH), 1 715 (C=O), 1 615, 1 545, 1 460, 1 450, and 1 425 cm^{-1} (C=C); δ[$(CD_3)_2SO$] 2.45—3.18 (4 H, m, CH_2CH_2), 5.48 (2 H, s, $ArCH_2$), 6.84 (1 H, apparent s, py-H), 6.95 (1 H, dd, *J* 5.0 and 1.5 Hz, py-H), 7.26—7.73 (5 H, m, ArH), 8.17 (1 H, d, *J* 5.0 Hz, py-H), and 8.82 (1 H, br s, CO_2H).

Methyl 3-(2-Benzyloxy-4-pyridyl)propionate (**18**).—A mixture of the acid (**17**) (70 g, 0.27 mol) in methanol (250 ml) was heated to effect complete solution. The resulting solution was cautiously treated with concentrated sulphuric acid (17 ml), and the reaction mixture was heated under reflux for 2.5 h. After this time the mixture was cooled and concentrated under reduced pressure to *ca.* 80 ml, and then quenched into water (300 ml). The aqueous mixture was basified to pH 10 and extracted with dichloromethane (1 × 250 ml + 2 × 100 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the *title compound* (**18**) (62 g, 84%) as a pale yellow oil which crystallised with time; b.p. 200 °C at 0.2 mmHg (Found: C, 70.7; H, 6.5; N, 5.0. $C_{16}H_{17}NO_3$ requires C, 70.8; H, 6.3; N, 5.2%); $\nu_{max.}$(liq. film) 3 030, 2 950 (C–H), 1 740 (C=O), 1 615, 1 560, and 1 420 cm^{-1} (C=C); δ 2.40—3.08 (4 H, m, CH_2CH_2), 3.68 (3 H, s, CO_2Me), 5.46 (2 H, s, $ArCH_2$), 6.73 (1 H, apparent s, py-H), 6.80 (1 H, dd, *J* 5.0 and 1.5 Hz), 7.25—7.66 (5 H, m, ArH), and 8.17 (1 H, d, *J* 5.0 Hz, py-H).

2-(2,5-*Dimethylpyrrol*-1-*yl*)-4-*methylpyridine* (**19**).—A mixture of 2-amino-4-methylpyridine (**3**) (160 g, 1.48 mol), toluene (1 l), glacial acetic acid (130 ml), and acetonylacetone (252 g, 2.20 mol) was heated under reflux with water separation *via* a Dean and Stark trap. After 18 h the reaction mixture was cooled and the toluene removed under reduced pressure. The dark coloured liquid was treated with 10% aqueous hydrochloric acid. After stirring for 1 h, the pH was adjusted to pH 8 with 40% w/v aqueous sodium hydroxide and the resulting mixture was stirred and cooled to 0—5 °C. The mixture was then filtered and the filter cake was washed with cold water and dried at 50 °C *in vacuo* to give a brown amorphous solid (196.6 g). More brown amorphous solid (34 g) was obtained from the mother liquors. Recrystallisation from methanol–water (2:1) gave the *title compound* (**19**) (161 g, 58%), m.p. 69—71 °C (MeOH–water, 2:1) (Found: C, 77.3; H, 7.5; N, 15.1. $C_{12}H_{14}N_2$ requires C, 77.4; H, 7.6; N, 15.0%); $\nu_{max.}$ 1 600, 1 545, 1 515, and 1 470 cm^{-1} (C=C); δ 2.14 (6 H, s, pyrr-Me), 2.40 (3 H, s, py-Me), 5.96 (2 H, s, pyrr-H), 7.13 (1 H, s, py-H), 7.23 (1 H, d, *J* 5.0 Hz, py-H), and 8.60 (1 H, d, *J* 5.0 Hz, py-H).

Alkylation of the Methylpyridine (**19**) *with Sodium Chloroacetate.*—Liquid ammonia (1.5 l) was placed in a 3 l flask fitted with a mechanical stirrer and solid CO_2–acetone condenser. Sodium metal (14.8 g, 0.64 mmol) was added followed by a few crystals of iron(III) nitrate. The resulting dark mixture was stirred for 20 min, then treated with the methylpyridine (**19**) (80 g, 0.43 mol) and stirred for a further 30 min. The resulting dark reaction mixture was cautiously treated with sodium chloroacetate (50 g, 0.43 mol) and stirred for a further 3.5 h. After this time ammonium chloride (35 g, 0.65 mol) was added. Ammonia was allowed to evaporate and the residue was dissolved in water (1 l) and extracted with dichloromethane (3 × 250 ml). The aqueous layer was acidified to pH 6.5 with 10% aqueous hydrochloric acid. After cooling, the fawn coloured solid was filtered off and the filter cake was washed with water and dried at 50 °C *in vacuo* to give 3-[2-(2,5-*dimethylpyrrol*-1-*yl*)-4-*pyridyl*]*propionic acid* (**20**) (66.6 g, 63%) as an amorphous fawn coloured solid which was very difficult to crystallise and so was used without further purification; m.p. 135 °C (decomp.) (Found: M^+, 244.1200. $C_{14}H_{16}N_2O_2$ requires M, 244.1212); $\nu_{max.}$ 1 710 (C=O), 1 610, 1 550, 1 480, 1 460, and 1 435 cm^{-1} (C=C); δ(CD_3OD) 2.1 (6 H, s, pyrr-Me), 2.48—3.32 (4 H, m, CH_2CH_2), 5.93 (2 H, s, pyrr-H), 7.37 (1 H, apparent s, py-H), 7.48 (1 H, dd, *J* 5.0 and 1.5 Hz, py-H), and 8.58 (1 H, d, *J* 5.0 Hz, py-H); *m/z* 244 (M^+, 100), 243 (71, M − H), 229 (40, M − Me), 183 (13), and 94 (57).

Esterification of the Acid (**20**).—A solution of the acid (**20**) (50.1 g, 0.21 mol) in methanol (500 ml) was treated with concentrated sulphuric acid (35 ml). The resulting solution was refluxed for 3.5 h and then cooled. The reaction mixture was concentrated under reduced pressure to *ca.* 100 ml and then poured into water (300 ml). The aqueous mixture was basified to pH 10 with aqueous 0.880 ammonia and extracted with dichloromethane (3 × 150 ml). The combined dichloromethane layers were dried ($MgSO_4$) and evaporated to give *methyl* 3-[2-(2,5-*dimethylpyrrol*-1-*yl*)-4-*pyridyl*]*propionate* (**21**) (49 g, 93%) as a very air-sensitive dark coloured oil which defied attempts to be purified by distillation and was stored cold under nitrogen; b.p. 200 °C at 0.1 mmHg (Found: M^+, 258.1380. $C_{15}H_{18}N_2O_2$ requires M, 258.1368); $\nu_{max.}$(liq. film) 1 740 (C=O), 1 600, 1 550, 1 520, 1 475, and 1 430 cm^{-1} (C=C); δ 2.12 (6 H, s, pyrr-Me), 2.50—3.30 (4 H, m, CH_2CH_2), 3.73 (3 H, s, CO_2Me), 6.03 (2 H, s, pyrr-H), 7.20 (1 H, apparent s, py-H), 7.30 (1 H, dd, *J* 5.0 and 1.5 Hz, py-H), and 8.70 (1 H, d, *J* 5.0 Hz, py-H); *m/z* 258 (M^+, 100), 257 (61, M − H), 243 (38, M − Me), 180 (23), 121 (37), and 94 (57).

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