Synthesis of 2-Substituted 4-Pyridylpropionates. Part 1. Claisen Condensation Approach

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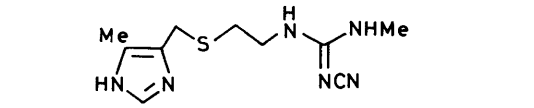
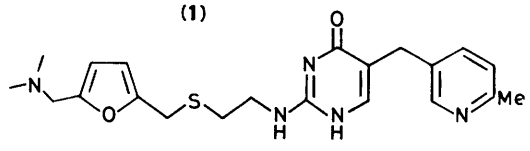
A synthesis of methyl 3-(2-methoxy-4-pyridyl)propionate (**4**), a key intermediate in the synthesis of the potent and long-acting histamine H_2-receptor antagonist SK&F 93574 (**3**), is described. The key steps in the synthesis of compound (**4**) are a Claisen ester condensation to give the intermediate (**16**) and a subsequent reduction step to give the ester (**4**). The reduction was found to be difficult and our investigations are described. In addition, alternative, but unsuccessful, approaches to the desired pyridylpropionate (**4**) are discussed.

Many people in the developed world suffer from stress related gastrointestinal mucosal damage. In the mid-1970's Smith Kline and French introduced the anti-ulcer drug Cimetidine (Tagamet) (**1**), a histamine H_2-receptor antagonist. This class of drugs blocks the action of histamine in stimulating gastric acid secretion.[1] Since the discovery of H_2-receptor antagonists more than two further products, such as Glaxo's Ranitidine (Zantac) and Yamanouchi's Famotidine, have been introduced onto the market.

Following the introduction of Cimetidine (**1**), research was carried out to find a potent and long-acting H_2-receptor antagonist. Among the second generation compounds identified were SK&F 93479 (**2**)[2] and SK&F 93574 (**3**),[3] which both contain a pyridylmethyl-substituted isocytosine moiety. A description of the synthesis of SK&F 93479 (**2**) has been published[2] and, based on considerable work carried out on the construction of the isocytosine moiety in (**2**), a key intermediate in the synthesis of (**3**) was identified as methyl 3-(2-methoxy-4-pyridyl)propionate (**4**). We therefore required an efficient synthesis of large quantities of this intermediate. This paper describes an approach to the key intermediate (**4**) *via* a Claisen ester condensation, and the following paper describes an alternative approach used for large-scale preparations.



(**1**)



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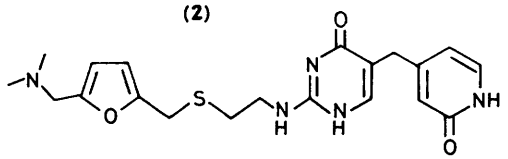
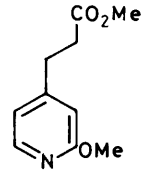


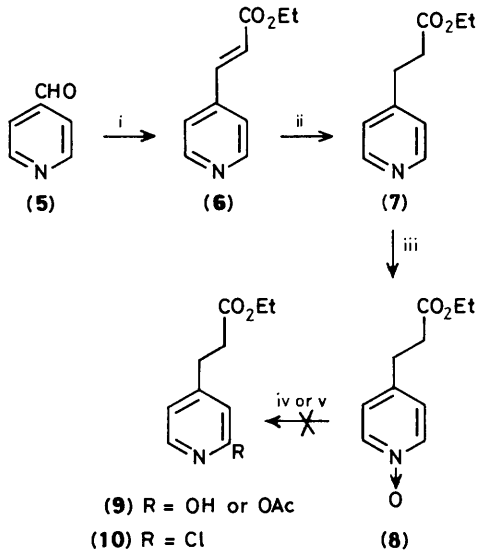
(**3**)



(**4**)

Results and Discussion

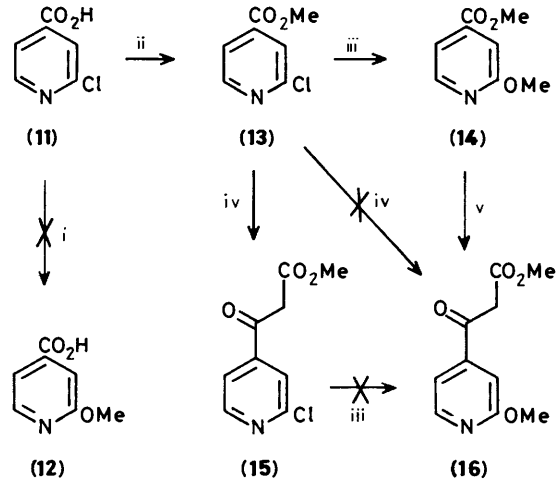
Owing to the paucity of commercially available 2,4-disubstituted pyridines, isonicotinaldehyde (**5**) was chosen as a starting material for initial investigations (Scheme 1). Thus treatment of aldehyde (**5**) with the anion of ethyl acetate gave the unsaturated ester (**6**) which on catalytic hydrogenation gave ethyl 3-(4-pyridyl)propionate (**7**) in good yield. Subsequent treatment of ester (**7**) with 30% hydrogen peroxide in glacial acetic acid gave the corresponding *N*-oxide (**8**) in 76% yield.



Scheme 1. *Reagents and conditions:* i, NaOMe, $MeCO_2Et$, 75%; ii, 10% Pd–C,H_2, EtOH, 90%; iii, H_2O_2–$MeCO_2H$, 100 °C, 76%; iv, $POCl_3$, $SOCl_2$, or PCl_5–$POCl_3$, reflux; v, Ac_2O, reflux

Surprisingly, all of our attempts to carry out the well known Katada rearrangement[4,5] with acetic anhydride, $POCl_3$, $SOCl_2$, or PCl_5–$POCl_3$ on the *N*-oxide (**8**) to give the corresponding pyridine (**9**) or the chloropyridine (**10**)[6] failed.

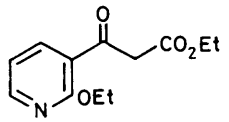
Since the route illustrated in Scheme 1 failed to furnish compound (**4**), attention was focussed on using commercially available 2-chloroisonicotinic acid (**11**) as starting material as shown in Scheme 2. Attempts to prepare 2-methoxyisonicotinic acid (**12**) from (**11**) by methoxide displacement in dimethylformamide (DMF) failed. A related transformation using sodium ethoxide is reported in the literature;[7] however, an autoclave was used.



Scheme 2. *Reagents and conditions:* i, NaOMe; ii, $SOCl_2$ then MeOH, 72%; iii, NaOMe, dioxane, reflux, 76%; iv, NaOMe, $MeCO_2Me$, reflux, 76%; v, NaH, $MeCO_2Me$, DMF, room temp., 80%

Treatment of compound (**11**) with thionyl chloride followed by work-up with methanol gave the desired methyl 2-chloroisonicotinate (**13**). Treatment of ester (**13**) with sodium methoxide in DMF gave a mixture of compounds (**11**) and (**12**) as the only isolated products. De-esterification occurred due to the presence of sodium chloride,[8] the by-product from methoxide displacement. The rate of de-esterification is presumably comparable with that for methoxide displacement thus giving rise to the observed mixture. Reduction of carboxylic acids directly to the corresponding aldehyde using bis(*N*-methylpiperazinyl)aluminium hydride has been reported recently.[9] Reduction of pyridinecarboxylic acids, however, is complicated owing to the possibility of reducing the pyridine nucleus. Reduction of (**12**) to 2-methoxyisonicotinaldehyde was investigated, and although partial conversion into the desired product occurred, the isolated material was contaminated with *N*-methylpiperazine and other by-products. Reduction of aromatic acid chlorides to the corresponding aldehyde with bis(triphenylphosphine)copper(I) tetrahydroborate has been achieved in high yield.[10] This methodology applied to the acid chlorides of (**11**) and (**12**) also failed to furnish the desired 4-carbaldehyde derivatives, thus an alternative approach to the synthesis of ester (**4**) was investigated.

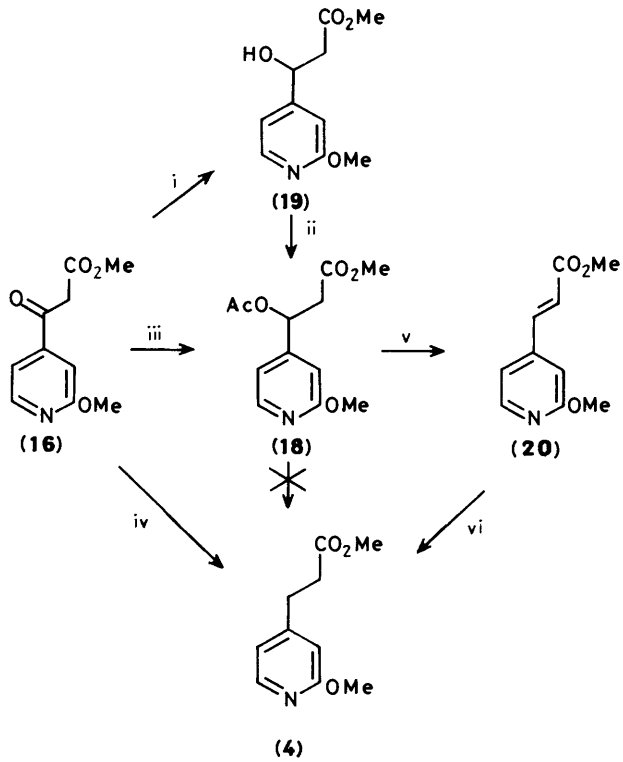
Treatment of ester (**13**) with sodium methoxide in refluxing methanol[11] gave partial conversion into the desired methyl 2-methoxyisonicotinate (**14**) in low yield, and surprisingly changing the solvent to dioxane led to the isolation of (**14**) in good yield. Several examples of Claisen condensation on pyridine compounds have been described.[12–14] Claisen condensation of the intermediates (**13**) and (**14**) with the anion of methyl acetate was investigated. Treatment of compound (**13**) with sodium methoxide in refluxing methyl acetate gave the desired condensation product (**15**) in good yield without displacement of the chlorine moiety. N.m.r. analysis of the product in $CDCl_3$–$[(CD_3)_2SO]$ gave methyl resonances at δ 3.68 and 3.77, in addition to resonances at δ 4.00 and 5.78, and two doublets at δ 8.48 and 8.65. These signals are consistent with the desired product in both the keto and enol forms in a ratio of 1:1.8 by integration. Surprisingly, all attempts to displace the 2-chloro moiety of (**15**) with sodium methoxide in refluxing dioxane, methanol, or tetrahydrofuran failed. One literature report[14] describes the direct conversion of ethyl 2-chloronicotinate into the product (**17**) by a Claisen condensation presumably using sodium ethoxide as the base,



(**17**)

although no experimental details are given in the paper. Attempts to repeat this reaction using (**13**) as the substrate and sodium methoxide as the base failed to give the product (**16**). Preparation of the desired Claisen condensation product (**16**) requires particular experimental conditions. Methyl 2-methoxyisonicotinate (**14**) is treated with sodium hydride and methyl acetate in DMF at ambient temperature. The product is then extracted into 40% aqueous hydrochloric acid and base released to give methyl 3-oxo-3-(2-methoxy-4-pyridyl)propionate (**16**) in 70—80% yield. N.m.r. analysis of the product in $CDCl_3$ indicated that the product exists in the keto and enol forms in a ratio of 1:1.2 by integration. The methyl ether and one of the methyl ester resonances are coincident at δ 3.95.

Following the successful preparation of compound (**16**), reduction to the key intermediate (**4**) was investigated (Scheme 3). Based on experience gained during the synthesis of

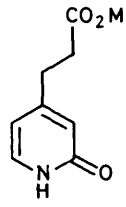


Scheme 3. *Reagents and conditions:* i, $NaBH_4$, MeOH, room temp., 79%; ii, Ac_2O, DMAP, CH_2Cl_2, room temp., 86%; iii, 10% Pd–C, H_2, AcOH, 55 °C then Ac_2O, DMAP, toluene, room temp., 90%; iv, Zn, HCO_2H, reflux, 40%; v, DBU, room temp., 66%; vi, 10% Pd–C, H_2, MeOH, 90%

compound (**2**),[2] a two-stage reduction sequence, *via* the acetoxy derivative (**18**) was first attempted. Reduction to the hydroxy ester (**19**) was facile using 10% Pd–C in glacial acetic acid at 55 °C; alternatively sodium borohydride in methanol can be used. Acetylation can be carried out in toluene or dichloromethane using acetic anhydride and catalytic amounts of 4-dimethylaminopyridine to give compound (**18**). Attempts

to effect hydrogenolysis of the propionate (**18**) to give the desired product (**4**) using 10% Pd–C in glacial acetic acid at 65 °C with or without added mineral acid failed. In addition, it was found that more forcing conditions resulted in reduction of the pyridine nucleus. Several methods for the conversion of aromatic ketones into alkyl arenes are reported in the literature, and attempts to convert (**16**) into the pyridylpropionate (**4**) directly were made. Hydrogenation with Pd–C or Rh–C in glacial acetic acid at 65 °C at 50 p.s.i. with or without iron(III) chloride or mineral acid led to facile reduction to compound (**19**), but further reduction to the pyridylpropionate (**4**) was not observed.

The same result was obtained under catalytic transfer hydrogenolysis conditions using iron(III) chloride and Pd–C in the presence of cyclohexane or limonene.[15] Reduction using zinc and formic acid[16] was found to give compound (**4**) directly from (**16**); however, this procedure suffered from some drawbacks. It was found that the quality of zinc powder used was crucial for reduction to occur, and best results were obtained with 325 mesh zinc powder. Several equivalents of zinc are required for the reaction to proceed to completion and the long reaction times lead to the formation of variable quantities of an impurity which shows resonances at δ 6.16 (d), 6.38 (s), and 7.30 (d) in the ^{1}H n.m.r. spectrum. These data are consistent with the impurity arising from acid-catalysed demethylation of the methyl ether to give the corresponding pyridone (**21**). The crude product therefore requires distillation before further transformations are carried out. Consistently good yields were not



(**21**)

obtained in this reaction. Although on one occasion a yield of 73% was obtained using 1 g of the keto ester (**16**), the yield dropped dramatically on scale up to 5 g. These drawbacks render the reaction unsuitable for large-scale preparations of the desired pyridylpropionate (**4**).

Investigation of an alternative approach revealed that the acetoxy moiety of (**18**) could be eliminated to give compound (**20**) using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base, followed by catalytic hydrogenation to give the pyridylpropionate (**4**).

In conclusion, two routes to methyl 3-(2-methoxy-4-pyridyl)-propionate (**4**) have been developed, giving an overall yield from the acid (**11**) of 18% *via* zinc–formic acid reduction and 23% *via* DBU elimination. In addition to length, capricious reduction, or use of an expensive reagent, both routes suffer from a major drawback for large-scale preparations of (**4**) in that the hazardous mixture of sodium hydride–DMF[2] is used. Alternative approaches to the synthesis of compound (**4**) were therefore investigated and are discussed in the following paper.

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 obtained 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, Jeol GX270, or Bruker AM250 instrument, and mass spectra were recorded on a VG 7070F spectrometer. 2-Chloroisonicotinic acid (**11**) was obtained from Reilly Tar and Chemical Corporation.

Methyl 2-Chloroisonicotinate (**13**).—2-Chloroisonicotinic acid (**11**) (93.1 g, 0.59 mol) was added to a solution of thionyl chloride (83 ml, 1.14 mol) in toluene (50 ml). The reaction mixture was heated under reflux until gas evolution ceased. The reaction mixture was then cooled and treated cautiously with a solution of methanol (68 ml, 1.65 mol) in toluene (20 ml) and the resulting slurry was heated under reflux, whereupon complete solution was obtained. The reaction mixture was cooled, poured into water (100 ml), and basified to pH 12 using 40% aqueous sodium hydroxide. The organic layer was separated, and the aqueous layer was extracted with toluene (3 × 50 ml). The combined toluene layers were distilled to give an oil (85 g) which was distilled to give the title compound (**13**) (73 g, 72%) as a colourless oil which crystallised with time, b.p. 52—56 °C at 0.05 mmHg (lit.,[17] 84—88 °C at 15 mmHg) (Found: C, 48.6; H, 3.6; N, 8.1%. Calc. for $C_7H_6ClNO_2$: C, 49.0; H, 3.5; N, 8.2%); $\nu_{max.}$(liq. film) 3 100, 3 080 (ArCH), 1 735 (C=O), 1 590, 1 550, and 1 460 cm^{-1} (C=C); δ 3.95 (3 H, s, OMe), 7.71—8.0 (2 H, m, ArH), and 8.61 (1 H, d, *J* 5 Hz, ArH).

Methyl 2-Methoxyisonicotinate (**14**).—Methyl 2-chloroisonicotinate (**13**) (50 g, 0.29 mol) was dissolved in dry dioxane (100 ml) and treated with sodium methoxide (24 g, 0.44 mmol). The resulting reaction mixture was stirred at reflux for 1 h, then cooled to room temperature, and poured into water (1 l). The aqueous mixture was extracted with dichloromethane (4 × 200 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give an oil which was distilled under reduced pressure to give the *title compound* (**14**) (37 g, 76%) as a pale yellow oil, b.p. 120 °C at 1 mmHg (Found: C, 56.3; H, 5.3; N, 8.1. $C_8H_9NO_3$ requires C, 57.5; H, 5.4; N, 8.4%); $\nu_{max.}$(liq. film) 2 980, 2 950 (ArCH), 1 735 (C=O), 1 610, 1 562, 1 481, and 1 450 cm^{-1} (C=C); δ 3.99 (3 H, s, CO_2Me), 4.01 (3 H, s, OMe), 7.38—7.60 (2 H, m, ArH), and 8.46 (1 H, d, *J* 5 Hz, ArH).

Claisen Condensation of Methyl 2-Chloroisonicotinate (**13**).—A solution of methyl 2-chloroisonicotinate (**13**) (2.0 g, 12 mmol) in methyl acetate (20 ml) was treated with sodium methoxide (0.96 g, 18 mmol). The resulting mixture was refluxed for 1.75 h. The reaction mixture was added to water (75 ml) and acidified to pH 7 with 10% aqueous hydrochloric acid. The aqueous mixture was saturated with solid sodium chloride and extracted with ethyl acetate (3 × 40 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give *methyl 3-(2-chloro-4-pyridyl)-3-oxopropionate* (**15**) (1.9 g, 76%), as a pale yellow solid, m.p. 78—80 °C (from Pr^iOH) (Found: M^+, 213.018. $C_9H_8ClNO_3$ requires *M*, 213.019); $\nu_{max.}$ 1 736., 1 640 (C=O), 1 590, 1 539, 1 460, and 1 440 cm^{-1} (C=C); δ[$CDCl_3$ + $(CD_3)_2SO$] 3.68 (s, OMe-enol form), 3.77 (s, OMe-keto form), 4.00 (s, $COCH_2CO_2Me$), 5.78 (s, C=CH), 7.47—7.83 (m, ArH), 8.48 (d, *J* 5 Hz, ArH), and 8.65 (d, *J* 5 Hz, ArH). Ratio of keto:enol form 1:1.8; *m/z* 213/5 (M^+), 182/4 (30/10%), 181/3 (20/8, *M* − MeOH), 182/4 (15/6, *M* − OMe), 140/2 (100/30, *M* − CH_2CO_2Me), 112/4 (30/10, *M* − CH_2CO_2Me − CO), 85/7 (15/5), and 69 (25).

Claisen Condensation of Methyl 2-Methoxyisonicotinate (**14**).—Sodium hydride (2.9 g of a 60% suspension in oil, 72 mmol) was suspended in dry DMF (30 ml) and methyl 2-methoxyisonicotinate (**14**) (8.1 g, 48 mmol) was added. A solution of methyl acetate (5.6 g, 76 mmol) in DMF (20 ml) was added to the stirred mixture over 1 h. The reaction mixture was stirred at ambient temperature for 1.5 h and poured into water

(100 ml). The aqueous mixture was acidified with 10% aqueous hydrochloric acid to pH 7 and extracted with toluene (5 × 50 ml). The combined organic layers were washed with water (1 × 100 and 1 × 70 ml) and extracted with 40% aqueous hydrochloric acid (2 × 100 and 1 × 50 ml). The acidic extracts were basified with 40% w/v aqueous sodium hydroxide, extracted with dichloromethane (3 × 100 ml), and the combined dichloromethane layers dried ($MgSO_4$) and evaporated to give *methyl* 3-(2-*methoxy*-4-*pyridyl*)-3-*oxopropionate* (**16**) (8.0 g, 80%) as an off-white solid, m.p. 59—60 °C (from Pr^iOH) (Found: C, 57.0; H, 5.2; N, 6.6. $C_{10}H_{11}NO_4$ requires C, 57.4; H, 5.3; N, 6.7%); $\nu_{max.}$(liq. film) 3 010, 2 940 (CH), 1 740, 1 656 (C=O), 1 609, 1 598, 1 554, 1 482, and 1 448 cm^{-1} (C=C); δ 3.73 (s, $COCH_2CO_2Me$), 3.80 (s, OMe), 3.95 (s, OMe), 5.73 (s, C=CH), 7.12—7.41 (m, ArH), 8.31 (d, *J* 5 Hz, ArH), and 8.42 (d, *J* 5 Hz, ArH). Ratio of keto:enol form 1:1.2; *m/z* 209 (M^+, 82%) 208 (76, *M* − H), 177 (40, *M* − MeOH), 176 (48, *M* − MeOH − H), 147 (20), 136 (100, *M* − CH_2CO_2Me), 108 (66, *M* − CH_2CO_2Me − CO), 81 (34), 78 (23), and 51 (15).

Reduction of Compound (**16**) *with Sodium Borohydride.*—A solution of methyl 3-(2-methoxy-4-pyridyl)-3-oxopropionate (**16**) (7.5 g, 36 mmol) in methanol (100 ml) was cooled to 10 °C and treated with sodium borohydride (1.5 g, 36 mmol). After 0.5 h the solution was diluted with water (200 ml) and methanol was removed under reduced pressure. The aqueous residue was extracted with dichloromethane (3 × 100 ml), and the combined dichloromethane layers were dried ($MgSO_4$) and evaporated under reduced pressure to give *methyl* 3-*hydroxy*-3-(2-*methoxy*-4-*pyridyl*)*propionate* (**19**) (6 g, 79%) as a colourless oil which crystallised with time, m.p. 41—44 °C (Found: C, 56.9; H, 6.4; N, 6.6. $C_{10}H_{13}NO_4$ requires C, 56.9; H, 6.2; N, 6.6%); $\nu_{max.}$(liq. film) 3 400br (OH), 2 960 (CH), 1 740 (C=O), 1 620, 1 570, 1 480, 1 450, and 1 400 cm^{-1} (C=C); δ 2.70 (2 H, d, *J* 5.3 Hz, CH_2CO_2Me), 3.62 (1 H, br s, OH), 3.73 (3 H, s, CO_2Me), 3.94 (3 H, s, OMe), 5.77 (1 H, t, *J* 5.3 Hz, ArC*H*OH), 6.77 (1 H, d, *J* 2.8 Hz, ArH), 6.87 (1 H, dd, *J* 6.4 and 2.8 Hz, ArH), and 8.12 (1 H, d, *J* 6.4 Hz, ArH).

Methyl 3-*Acetoxy*-3-(2-*methoxy*-4-*pyridyl*)*propionate* (**18**).—A solution of methyl 3-hydroxy-3-(2-methoxy-4-pyridyl)-propionate (**19**) (5.0 g, 24 mmol) in dichloromethane (50 ml) was treated with acetic anhydride (3.4 ml, 36 mmol) followed by a few crystals of 4-dimethylaminopyridine. The reaction mixture was stirred at ambient temperature overnight. The dichloromethane solution was then washed with saturated aqueous sodium hydrogencarbonate (1 × 50 ml), water (1 × 50 ml), dried ($MgSO_4$), and evaporated to give the *title compound* (**18**) (5.2 g, 86%) as a colourless oil, b.p. 190 °C at 1.5 mmHg (Found: C, 57.0; H, 5.9; N, 5.5. $C_{12}H_{15}NO_5$ requires C, 57.0; H, 6.0; N, 5.5%); $\nu_{max.}$(liq. film) 2 960 (CH), 1 750 (C=O), 1 620, 1 570, 1 485, 1 455, and 1 405 cm^{-1} (C=C); δ 2.10 (3 H, s, OCOMe), 2.76 (1 H, dd, *J* 15.6 and 6.3 Hz, CH_2CO_2Me), 2.92 (1 H, dd, *J* 15.6 and 7.8 Hz, CH_2CO_2Me), 3.69 (3 H, s, CO_2Me), 3.92 (3 H, s, OMe), 6.09 (1 H, dd, *J* 7.8 and 6.3 Hz, $AcOCHCH_2$), 6.72 (1 H, d, *J* 2.3 Hz, ArH), 6.85 (1 H, dd, *J* 7.0 and 2.3 Hz, ArH), and 8.13 (1 H, d, *J* 7.0 Hz, ArH).

Catalytic Reduction of Compound (**16**) *Followed by Acetylation.*—A solution of methyl 3-(2-methoxy-4-pyridyl)-3-oxopropionate (**16**) (2.0 g, 9.5 mmol) in glacial acetic acid (20 ml) was treated with 10% palladium–charcoal (0.2 g, 50% wet with water) and hydrogenated at 50 p.s.i. and 55 °C. After 2 h the catalyst was filtered off and the solvent removed under reduced pressure to give a brown oil, $\nu_{max.}$ 3 400 (OH), 1 730 (C=O), 1 620, 1 560, 1 480, and 1 450 cm^{-1} (C=C). The crude oil was dissolved in toluene (15 ml) and treated with acetic anhydride (1.2 ml, 12.7 mmol) and a few crystals of 4-dimethylaminopyridine. The reaction mixture was stirred at ambient temperature overnight then washed with saturated aqueous sodium hydrogencarbonate (1 × 15 ml), water (1 × 15 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give methyl 3-acetoxy-3-(2-methoxy-4-pyridyl)propionate (**18**) (2.2 g, 90%) as an oil, b.p. 190 °C at 1.5 mmHg, spectroscopically identical with material produced by sodium borohydride reduction followed by acetylation.

Reduction of Compound (**16**) *Using Zinc in Formic Acid.*—A solution of methyl 3-(2-methoxy-4-pyridyl)-3-oxopropionate (**16**) (1.1 g, 5 mmol) in formic acid (10 ml) was treated with 325 mesh zinc powder (1.6 g, 25 mmol). The resulting mixture was stirred under reflux overnight. The reaction mixture was then cooled, filtered, and the solids were washed with formic acid (5 ml). The combined filtrates were diluted with water (30 ml) and basified with 0.880 aqueous ammonia (15 ml). The resultant mixture was extracted with dichloromethane (2 × 15 ml + 1 × 10 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give *methyl* 3-(2-*methoxy*-4-*pyridyl*)*propionate* (**4**) (0.4 g, 40%) as a pale yellow 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, 6.8; 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 2.65 (2 H, t, *J* 7.4 Hz, CH_2CH_2), 2.90 (2 H, t, *J* 7.4 Hz, CH_2CH_2), 3.69 (3 H, s, CO_2Me), 3.93 (3 H, s, OMe), 6.57 (1 H, d, *J* 1.0 Hz, ArH), 6.73 (1 H, dd, *J* 6.1 and 1.0 Hz, ArH), and 8.07 (1 H, d, *J* 6.1 Hz, ArH).

Methyl 3-(2-*methoxy*-4-*pyridyl*)*acrylate* (**20**).—Methyl 3-acetoxy-3-(2-methoxy-4-pyridyl)propionate (**18**) (0.5 g, 2 mmol) and DBU (0.33 g, 2.2 mmol) were mixed together and stirred at room temperature. After 15 min the precipitated solid was slurried with water (5 ml), filtered, washed with water, and dried *in vacuo* to give the *title compound* (**20**) (0.25 g, 66%) as a white solid, m.p. 71—73 °C (from Pr^iOH) (Found: C, 62.2; H, 5.7; N, 7.2. $C_{10}H_{11}NO_3$ requires C, 62.2; H, 5.7; N, 7.3%); $\nu_{max.}$ 1 720 (C=O), 1 650, 1 610, 1 560, and 1 490 cm^{-1} (C=C); δ 3.83 (3 H, s, CO_2Me), 3.95 (3 H, s, OMe), 6.54 (1 H, d, *J* 16.6 Hz, C=CH), 6.81 (1 H, d, *J* 1.4 Hz, ArH), 6.98 (1 H, dd, *J* 5.8 and 1.4 Hz, ArH), 7.56 (1 H, d, *J* 16.6 Hz, C=CH), and 8.18 (1 H, d, *J* 5.8 Hz, ArH).

Hydrogenation of Compound (**20**).—A solution of methyl 3-(2-methoxy-4-pyridyl)acrylate (**20**) (0.1 g, 0.5 mmol) in methanol (2 ml) was treated with 10% Pd–C (20 mg of a catalyst, 50% wet with water) and hydrogenated at 10 p.s.i. After 1 h the catalyst was filtered off and the solvent evaporated under reduced pressure to give methyl 3-(2-methoxy-4-pyridyl)propionate (**4**) (0.09 g, 90%) as an oil. The spectroscopic characteristics of the product were identical with a sample prepared *via* reduction of intermediate (**16**) using zinc in formic acid.

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References

1 T. H. Brown and R. C. Young, *Drugs Future*, 1985, **10**, 52.
2 T. Laird, *Chem. Ind.* (*London*), 1986, 134.
3 R. C. Blakemore, T. H. Brown, R. J. Chenery, G. J. Durant, C. R. Ganellin, M. E. Parsons, A. C. Rasmussen, and D. A. Rawlings, *Br. J. Pharmacol.*, 1985, **86**, (Proc. Suppl.), 570P.

4 A. McKillop and M. K. Bhagrath, *Heterocycles*, 1985, **23**, 1697.
5 K. Konno, K. Hashimoto, H. Shirahama, and T. Matsumoto, *Heterocycles*, 1986, **24**, 2169.
6 B. Bobranski, L. Kochanska, and A. Kowalewska, *Chem. Ber.*, 1938, **71**, 2385.
7 J. Buchi, P. Labhart, and L. Ragaz, *Helv. Chim. Acta*, 1947, **30**, 507.
8 A. P. Krapcho and A. J. Lovey, *Tetrahedron Lett.*, 1973, 957.
9 T. D. Hubert, D. P. Eyman, and D. F. Wiemar, *J. Org. Chem.*, 1984, **49**, 2279.
10 G. W. J. Fleet, C. J. Fuller, and P. J. C. Harding, *Tetrahedron Lett.*, 1978, 1437.
11 J. K. Seydel, K. J. Schaper, E. Wempe, and H. P. Cordes, *J. Med. Chem.*, 1976, **19**, 483.
12 G. R. Clemo and T. Holmes, *J. Chem. Soc.*, 1934, 1739.
13 H. G. Kolloff and J. Hunter, *J. Am. Chem. Soc.*, 1941, **63**, 490.
14 H. Sliwa and P. Mattie, *C.R. Seances Acad. Sci.*, 1964, **259**, 2255.
15 G. Brieger and T. H. Fu, *J. Chem. Soc., Chem. Commun.*, 1976, 757.
16 M. Ferles and A. Attia, *Collect. Czech. Chem. Commun.*, 1973, **38**, 611.
17 J. Baumler, E. Sorkin, and H. Erlenmeyer, *Helv. Chim. Acta*, 1951, **34**, 496.

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