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# THE SYNTHESIS OF 2-SUBSTITUTED-1,4-DIHYDROPYRIDINES

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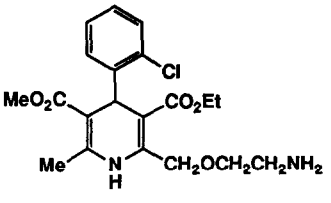
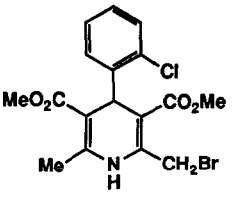
*Abstract: Reaction of the 2-hydroxymethyl-1,4-dihydropyridines 7 and 13 with $SO_2Cl_2$/imidazole followed by treatment with nucleophiles affords 2-substituted-1,4-dihydropyridines via the intermediacy of the 2-chloromethyl compounds 14 and 18, respectively.*

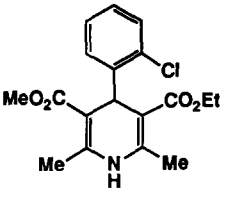
Calcium antagonists are now well established for the treatment of cardiovascular disease[1] and, of the classes of compound available with this mechanism of action, the 4-aryl-1,4-dihydropyridines have attracted the most attention[2,3]. Since the original discovery[4] of their therapeutically useful properties, many research groups have worked in this area. Our efforts were aimed at identifying 1,4-dihydropyridine derivatives with superior durations of action and bioavailabilities to existing agents and this work culminated in the identification of amlodipine (**1**)[5] which is currently in late stage clinical evaluation as a once a day treatment for angina[6] and hypertension[7]. As part of our synthetic programme, we required a general route to 2-substituted-1,4-dihydropyridines in order to explore the structure activity relationships for calcium antagonist activity. In a recent communication, we described[8] the formation of the 2-bromomethyl-1,4-dihydropyridine **2** and its in situ reaction with a range of nucleophiles. However, we required a general route to analogues containing different 3- and 5-esters as it is known[9] that 1,4-dihydropyridines with different 3- and 5-ester groups have greater potency than the corresponding compounds with identical 3- and 5-esters. As expected, reaction of **3** with pyridinium bromide perbromide followed by in situ reaction with nucleophiles gave mixtures of the two possible 2- and 6-regioisomeric products and we therefore investigated alternative routes to our target molecules.




**1,amlodipine**



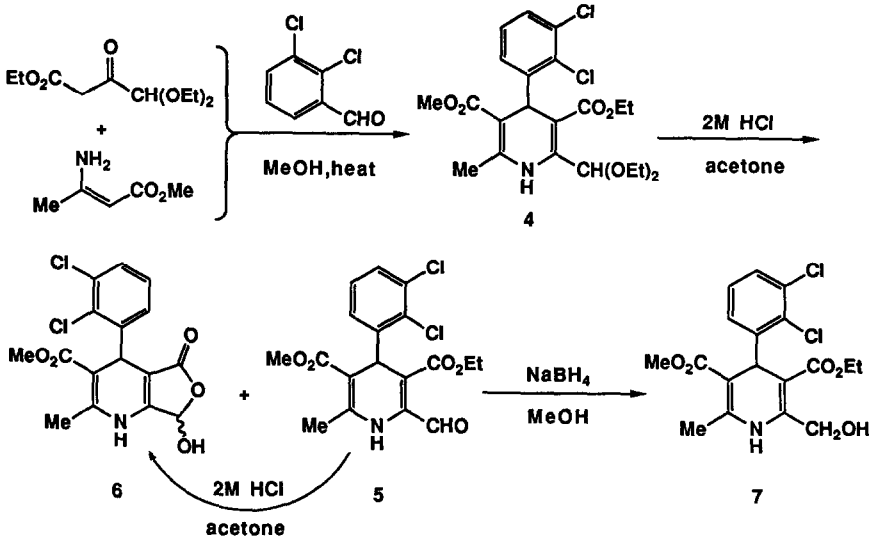

**2**




**3**

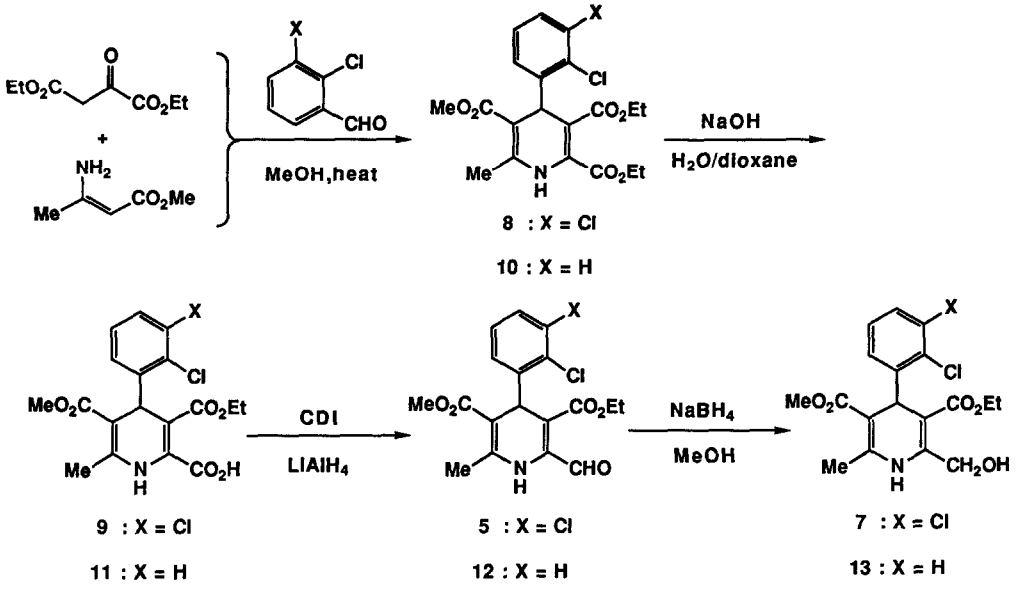
Results and Discussion

The direct synthesis of 2-chloromethyl-1,4-dihydropyridines by a Hantzsch condensation has recently been reported[10]. However, at the outset of our work we elected to prepare 2-hydroxymethyl-1,4-dihydropyridines in order to assess a range of possible leaving groups for displacement by appropriate nucleophiles. Hantzsch condensation of ethyl 4,4-diethoxyacetoacetate, methyl 3-aminocrotonate, and 2,3-dichlorobenzaldehyde gave the 2-diethoxymethyl derivative 4; the crude reaction mixture proved difficult to purify by chromatography and 4 could not, in our hands, be obtained in crystalline form. We therefore hydrolysed the partially purified 4 using 2M HCl in acetone to give the aldehyde 5[11]. This hydrolysis was accompanied by the formation of significant amounts of the corresponding aldehydo-acid whose $^1$H-NMR spectrum indicated it was present as the hydroxylactone tautomer 6. Acid-catalysed hydrolysis of 5 gave 6 directly. Reduction of 5 with $NaBH_4$ in MeOH according to the literature[12] afforded 7 in good yield.



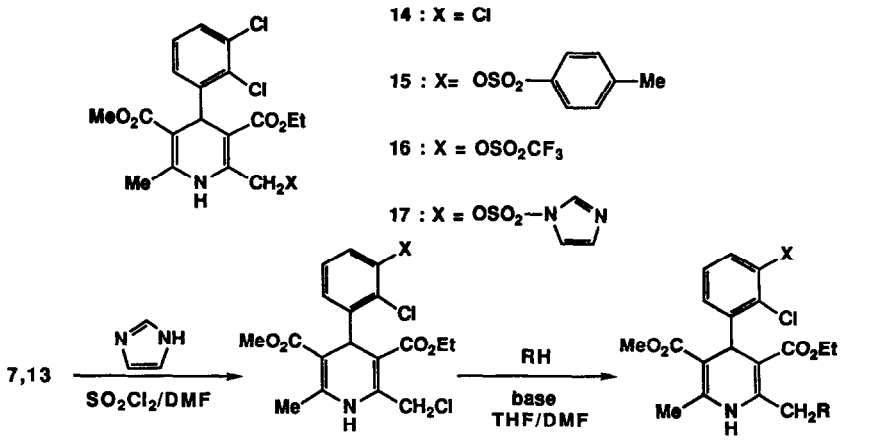

In view of the poor overall yield associated with the above route to the aldehyde 5 we developed an alternative route to the alcohol 7. Thus, Hantzsch condensation of diethyl 2-oxosuccinate, methyl 3-aminocrotonate, and 2,3-dichlorobenzaldehyde afforded the triester 8 which could be selectively hydrolysed[13] in situ to the 2-carboxylic acid 9 in good overall yield. Treatment of 9 with carbonyl diimidazole (CDI) followed by reduction of the intermediate imidazolide with excess $LiAlH_4$ gave a mixture of 5 and 7 in a ratio of approximately 3:1 (57% total yield after chromatography and crystallisation; the selective reduction of acid imidazolides to aldehydes with $LiAlH_4$ has been reported[14]). However, the alcohol 7 was obtained more conveniently by reduction of the crude mixture of 5 and 7 directly with $NaBH_4$ in MeOH; in this way the conversion of 9 to 7 was achieved in 61% yield.

In analogous fashion, Hantzsch condensation of diethyl 2-oxosuccinate, methyl 3-aminocrotonate, and 2-chlorobenzaldehyde followed by base-catalysed hydrolysis gave acid **11** via the triester **10**. Reaction of **11** with CDI followed by $LiAlH_4$ reduction afforded predominantely the aldehyde **12** together with some of the alcohol **13**. As above, reduction of this mixture with $NaBH_4$ in MeOH afforded **13** in 41% yield based on the acid **11**.




We now investigated the conversion of the hydroxy group in the alcohol **7** into a suitable leaving group. In our hands the reported[12] conversion of 2-hydroxymethyl-1,4-dihydropyridines into the corresponding 2-chloromethyl analogues using $CCl_4$ and $Ph_3P$ failed to produce **14** from **7**. Likewise attempts to prepare the tosylate **15** or triflate **16** analogues were also unsuccessful. However, Hanessian and Vatele[15] have developed the use of the imidazolylsulphonate leaving group as an alternative to triflate. We therefore treated the alcohol **7** with sulphuryl chloride and imidazole in DMF and observed by TLC its complete conversion within 5 minutes to a less polar, spot which is presumably the expected product **17**. However, more prolonged stirring caused the gradual disappearance of this fluorescent spot and the appearance of a new, less polar, material which, after work-up, was identified as **14** on the basis of a comparison of its $^1$H-NMR spectrum and TLC characteristics with those of authentic material[10]. Product **14** was not characterised analytically and showed a tendency to decompose on heating or prolonged standing.

Although we were able to isolate the 2-chloromethyl-1,4-dihydropyridine **14** we found it more convenient to react it in situ with nucleophiles. Thus, alcohol **7** was reacted with sulphuryl chloride and imidazole in DMF and the crude product **14** treated, after aqueous work-up, with a number of thiols in THF or THF/DMF solution in the presence of $K_2CO_3$ to give the thioethers **19-22** in acceptable yields. In similar fashion, treatment of the crude product **14** with pyridine-2-methanol/NaH in THF afforded the ether **23** in poor yield. Reaction of the 2-chlorophenyl analogue **13** as above, gave crude **18** which, after treatment with $HSCH_2CH_2NH_2/K_2CO_3$, afforded the amine **24** in good yield.




In conclusion, reaction of 2-hydroxymethyl-1,4-dihydropyridines with $SO_2Cl_2$/imidazole leads to 2-chloromethyl-1,4-dihydropyridines from which a range of 2-substituted-1,4-dihydropyridines can be synthesised. In addition, an efficient route to 2-hydroxymethyl-1,4-dihydropyridines has been identified.

## EXPERIMENTAL

Melting points were determined using a Büchi 510 melting point apparatus and are uncorrected. $^1$H-NMR spectra were recorded on a General Electric QE 300 spectrometer using $CDCl_3$ as the solvent. Column chromatography was performed on silica gel (Merck Kiesegel 60, 230-400 mesh). The structures of compounds were determined by $^1$H-NMR spectroscopy and microanalysis. Microanalytical data were not obtained on **14**, **19** and **21**; however, their $^1$H-NMR spectra were wholly compatible with their proposed structures and their purities were established by TLC.

4-(2,3-Dichlorophenyl)-3-ethoxycarbonyl-2-formyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine **5**. Route via acetal **4**. A solution of 2,3-dichlorobenzaldehyde (10.5 g, 60 mmol), ethyl 4,4-diethoxyacetoacetate (13.1 g, 60 mmol) and methyl 3-aminocrotonate (6.75 g, 59 mmol) in EtOH was heated under reflux for 16 h and evaporated. The residue was purified by chromatography using $CH_2Cl_2$ as eluant. Few of the fractions collected contained pure product - those fractions containing the acetal **4** were combined and evaporated. The residue was taken up in $Me_2CO$ (300 ml), treated with 2M HCl (150 ml) and stirred at room temperature for 16 h. The mixture was evaporated and the residue partitioned between EtOAc and water. The organic layer was washed with water, dried over $Na_2SO_4$ and evaporated. The residue was purified by chromatography using $CH_2Cl_2$ as the eluant. Appropriate fractions were combined and evaporated and the residue triturated with hexane. The resulting solid was collected, washed with hexane and dried to give compound **5** (4.00 g, 17%) as an orange powder, m.p. 128-130°C (lit.[11] m.p. 130°C) (Found: C, 54.4; H, 4.4; N, 3.2. $C_{18}H_{17}Cl_2NO_5$ requires: C, 54.3; H, 4.3; N, 3.5).

The column was then eluted with $CH_2Cl_2$ plus 2-4% MeOH. Appropriate fractions were combined and evaporated to give compound **6** (3.00 g, 25%) as a pale yellow powder, m.p. 138-141°C, whose spectral data and TLC characteristics were identical with those of authentic material.

Route from acid **9**. CDI (1.78 g, 11 mmol) was added in one portion to a solution of the acid **9** (4.14 g, 10 mmol) in THF (100 ml) and the mixture stirred at room temperature for 1.5 h, cooled to 0°C, treated with $LiAlH_4$ (0.58 g, 15 mmol), stirred with ice-cooling for 5 min, quenched by the cautious dropwise addition of saturated aqueous $NH_4Cl$ solution until a granular precipitate formed, filtered and evaporated. The residue was purified by chromatography using $CH_2Cl_2$ plus 0-5% EtOAc as eluant. Appropriate fractions were combined and evaporated and the residue triturated with hexane. The resulting solid was collected, washed with hexane and dried to give compound **5** (1.61 g, 43%) as an orange solid, m.p. 128-130°C, whose spectral data and TLC characteristics were identical with those of authentic material.

The column was then eluted with $CH_2Cl_2$ plus 10-50% EtOAc. Appropriate fractions were combined and evaporated to give compound 7 (0.56 g, 14%) as a colourless solid, m.p. 130-131°C, whose spectral data and TLC characteristics were identical with those of authentic material.

4-(2,3-Dichlorophenyl)-7-hydroxy-3-methoxycarbonyl-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine 6. A solution of the aldehyde 5 (275 mg, 0.69 mmol) in a mixture of $Me_2CO$ (8.5 ml) and 2M HCl (5.5 ml) was stirred at room temperature for 6 days and evaporated. The residue was purified by chromatography using $CH_2Cl_2$ plus 0-4% MeOH as eluant. Appropriate fractions were combined and evaporated and the residue crystallised from $CHCl_3$ to give compound 6 (158 mg, 62%) as a pale yellow solid, m.p. 140-142°C (Found: C, 51.6; H, 3.6; N, 3.7. $C_{16}H_{13}Cl_2NO_5$ requires: C, 51.9; H, 3.5; N, 3.8); $\delta_H$ 8.98 (1H, broad s), 7.20-7.45 (3H, m), 6.92 (1H, broad s), 6.10 (1H, broad s), 5.44 (1H, s), 3.50 (3H, s) and 2.43 (3H, s).

4-(2,3-Dichlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-2-hydroxymethyl-6-methyl-1,4-dihydropyridine 7. From aldehyde 5. $NaBH_4$ (46 mg, 1.3 mmol) was added to a stirred, ice-cooled solution of the aldehyde 5 (0.40 g, 1.0 mmol) in MeOH (10 ml) and the mixture stirred at 0°C for 15 min, quenched with 1M HCl and extracted into EtOAc. The organic extract was washed with water, dried over $Na_2SO_4$ and evaporated. The residue was crystallised from $Et_2O$ to give compound 7 (0.30 g, 75%) as a colourless powder, m.p. 130-131°C (Found: C, 54.15; H, 4.85; N, 3.2. $C_{18}H_{19}Cl_2NO_5$ requires: C, 54.0; H, 4.75; N, 3.5); $\delta_H$ 6.97-7.40 (4H, m), 5.45 (1H, s), 4.74 (2H, s), 4.10 (2H, q, J = 7Hz), 3.63 (3H, s), 2.35 (3H, s) and 1.20 (3H, t, J = 7Hz).

Direct from acid 9. CDI (17.8 g, 0.11 mol) was added portionwise over 15 min to a stirred, ice-cooled solution of the acid 9 (20.7 g, 50 mmol) in THF (300 ml) and the mixture stirred at 0°C for 1 h and at room temperature for 1 h. The mixture was cooled to 0°C, treated with $LiAlH_4$ (4.60 g, 0.12 mol) portionwise over 30 min, stirred at 0°C for 15 min, quenched cautiously by the dropwise addition of ice-cold 2M HCl and extracted into EtOAc. The organic extract was washed with 10% aqueous $Na_2CO_3$ solution and water, dried over $Na_2SO_4$ and evaporated. The residue was dissolved in MeOH (300 ml) and the solution treated portionwise over 10 min with $NaBH_4$ (4.60 g, 0.13 mol) with ice-cooling, stirred at 0°C for 15 min, quenched with ice-cold 2M HCl and extracted into EtOAc. The organic extracts were washed with water, dried over $Na_2SO_4$ and evaporated. The residue was crystallised from $Et_2O$ to give compound 7 (12.5 g, 61%) as a colourless powder, m.p. 130-131°C, whose spectral data and TLC characteristics were identical with those of authentic material.

2-Carboxy-4-(2,3-dichlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine **9**. A solution of 2,3-dichlorobenzaldehyde (224 g, 1.28 mol), diethyl 2-oxosuccinate (270 g, 1.29 mol), and methyl 3-aminocrotonate (150 g, 1.30 mol) in MeOH (2.05 l) was heated under reflux for 6 h and evaporated. The residue was dissolved in dioxane (800 ml), treated with a solution of NaOH (60 g, 1.5 mol) in water (800 ml), stirred at room temperature for 24 h and evaporated. The residue was partitioned between EtOAc and water and the aqueous layer washed with EtOAc, acidified with conc. HCl and extracted into EtOAc. The organic extracts were dried over $MgSO_4$ and evaporated. The residue was triturated with $Et_2O$ and the resulting solid collected, washed with $Et_2O$ and dried to give compound **9** (318 g, 60%) as a pale yellow powder, m.p. 160-162°C, which was characterised as a hemihydrate (Found: C, 51.6; H, 4.2; N, 3.5. $C_{18}H_{17}Cl_2NO_6$ .$0.5H_2O$ requires: C, 51.6; H, 4.1; N, 3.3); $\delta_H$ 8.00 (1H, s), 7.30-7.41 (2H, m), 7.18 (1H, t, J = 8Hz), 5.73 (1H, s), 4.30-4.44 (2H, m), 3.71 (3H, s), 2.42 (3H, s), 1.5-2.0 (1H, broad s) and 1.33 (3H, t, J = 7Hz).

2-Carboxy-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine **11**. A solution of 2-chlorobenzaldehyde (16.1 g, 0.114 mol), diethyl 2-oxosuccinate (21.5 g, 0.114 mol), and methyl 3-aminocrotonate (13.15 g, 0.114 mol) in MeOH (180 ml) was heated under reflux for 16 h and evaporated. The residue was dissolved in dioxane (160 ml), treated with a solution of NaOH (8.0 g, 0.20 mol) in water (70 ml), stirred at room temperature for 16 h and evaporated. The residue was worked up as described above to give compound **11** (22.0 g, 51%) as a pale yellow powder, m.p. 167-169°C. (Found: C, 56.9; H, 4.8; N, 3.8. $C_{18}H_{18}ClNO_6$ requires: C, 56.9; H, 4.7; N, 3.7); $\delta_H$ 8.61 (1H, s), 7.00-7.40 (3H, m), 5.30 (1H, s), 4.04 (2H, q, J = 7Hz), 3.53 (3H, s), 2.32 (3H, s) and 1.14 (3H, t, J = 8Hz).

4-(2-Chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-2-hydroxymethyl-6-methyl-1,4-dihydropyridine **13**. CDI (1.78 g, 11 mmol) was added in one portion to a stirred, ice-cooled solution of the acid **11** (3.80 g, 10 mmol) in THF (60 ml) and the mixture stirred at 0°C for 2 h, treated with $LiAlH_4$ (0.46 g, 12 mmol) portionwise over 5 min, stirred at 0°C for 15 min, quenched by the cautious dropwise addition of ice-cold 2M HCl and extracted into EtOAc. The organic extract was washed with 10% aqueous $Na_2CO_3$ solution and water, dried over $Na_2SO_4$ and evaporated. The residue (TLC indicates this to be a mixture of **12** and **13**) was dissolved in MeOH (60 ml) and the solution treated with $NaBH_4$ (0.46 g, 13 mmol) at 0°C, stirred at 0°C for 15 min, quenched into ice-cold 2M HCl and extracted into EtOAc. The organic extract was washed with water, dried over $Na_2SO_4$ and evaporated. The residue was purified by chromatography using $CH_2Cl_2$ plus 0-3% MeOH as eluant. Appropriate fractions were combined and evaporated and the residue crystallised from $Et_2O$ to give compound **13** (1.5 g, 41%) as a pale yellow powder, m.p. 124-125°C (Found: C, 59.1; H, 5.5; N, 3.8. $C_{18}H_{20}ClNO_5$ requires: C, 59.2; H, 5.5; N, 3.8); $\delta_H$ 6.97-7.50 (4H, m), 5.43 (1H, s), 4.77 (2H,

s), 4.09 (2H, q, J = 7Hz), 3.65 (3H, s), 2.34 (3H, s) and 1.20 (3H, t, J = 7Hz).

2-Chloromethyl-4-(2,3-dichlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine **14**. Route via Hantzsch Synthesis. A solution of 2,3-dichlorobenzaldehyde (175 mg, 1.0 mmol), ethyl 4-chloroacetoacetate (164 mg, 1.0 mmol) and methyl 3-aminocrotonate (115 mg, 1.0 mmol) in MeOH (40 ml) was heated under reflex for 3 h and evaporated. The residue was purified by chromatography using $CH_2Cl_2$ plus 0-5% EtOAc as eluant. Appropriate fractions were combined and evaporated to give compound **14** (166 mg, 40%) as a colourless foam. δH 7.33 (1H, d, J = 8Hz), 7.31 (1H, d, J = 8Hz), 7.10 (1H, t, J = 8Hz), 6.46 (1H, s), 5.53 (1H, s), 4.94 (2H, AB), 4.07 (2H, q, J = 7Hz), 3.62 (3H, s), 2.39 (3H, s) and 1.23 (3H, t, J = 7Hz).

Route from Alcohol **7**. A solution of $SO_2Cl_2$(0.20 ml; 2.5 mmol) in DMF (3 ml) was added dropwise over 5 min to a stirred, ice-cooled solution of **7** (0.50 g, 1.25 mmol) and imidazole (0.22 g, 3.2 mmol) in DMF (6 ml) and the mixture was stirred at room temperature for 1.5 h, diluted with EtOAc, washed with water, dried over $MgSO_4$ and evaporated to give compound **14** whose spectral data and TLC characteristics were identical with those of authentic material.

2-(2-Aminoethylthiomethyl)-4-(2,3-dichlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine **19**. Reaction of $SO_2Cl_2$ (4.05 g, 30 mmol) in DMF (40 ml) with a solution of **7** (6.00 g, 15 mmol) and imidazole (2.55 g, 37.5 mmol) in DMF (80 ml) and work-up as described above afforded crude **14**. A solution of this product in THF (50 ml) was added to a mixture of $HSCH_2CH_2NH_2$ HCl (4.26 g, 37.5 mmol) and $K_2CO_3$ (10.4 g) THF (50 ml) and DMF (50 ml), stirred at room temperature for 3 days and evaporated. The residue was partitioned between EtOAc and water and the organic layer washed with water, dried over $MgSO_4$ and evaporated. The residue was purified by chromatography using $CH_2Cl_2$ plus 0-10% MeOH as eluant. Appropriate fractions were combined and evaporated to give compound **19** (3.50 g, 51%) as a pale yellow oil; $\delta_H$ 7.00-7.45 (4H, m), 5.49 (1H, s), 4.02-4.20 (2H, m), 4.05 (2H, s), 3.61 (3H, s), 2.96 (2H, t, J = 7Hz), 2.64 (2H, t, J = 7Hz), 2.36 (3H, s), 1.70 (2H, s) and 1.22 (3H, t, J = 7Hz).

4-(2,3-Dichlorophenyl)-3-ethoxycarbonyl-2-(2-hydroxyethylthiomethyl)-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine **20**. Reaction of $SO_2Cl_2$ (0.80 ml; 10 mmol) in DMF (15 ml) with a solution of **7** (2.00 g, 5.0 mmol) and imidazole (0.85 g, 12.5 mmol) in DMF (30 ml) and work-up as described above afforded crude **14**. Reaction of a solution of **14** in THF (15 ml) and DMF (15 ml) with $HSCH_2CH_2OH$ (0.95 ml; 13.5 mmol) and $K_2CO_3$ (2.0 g) in THF (15 ml) and DMF (15 ml) and work-up as described above gave, after crystallisation of the residue from di-isopropyl ether, compound **20** (0.60 g, 26%) as pale yellow crystals,

m.p. 125°C (Found: C, 52.1; H, 5.0; N, 3.0. $C_{20}H_{23}Cl_2N\,O_5S$ requires: C, 52.2; H, 5.0; N, 3.0); $\delta_H$ 7.61 (1H, s), 7.52 (1H, dd, J = 8 and 2Hz), 7.48 (1H, dd, J = 8 and 2Hz), 7.29 (1H, t, J = 8Hz), 5.74 (1H, s), 4.26-4.40 (2H, m), 4.23 (2H, AB), 4.05 (2H, s), 3.83 (3H, s), 3.42 (1H, t, J = 6Hz, exchangeable with $D_2O$), 2.94 (2H, d, J = 7Hz), 2.56 (3H, s) and 1.41 (3H, t, J = 7Hz).

4-(2,3-Dichlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-2-(methoxycarbonyl methylthio)methyl-6-methyl-1,4-dihydropyridine **21**. Reaction of $SO_2Cl_2$ (0.27 g, 2.0 mmol) in DMF (10 ml) with a solution of **7** (0.40 g, 1.0 mmol) and imidazole (0.68 g, 10 mmol) in DMF (5 ml) and work-up as described above afforded crude **14**. Reaction of a solution of **14** in THF (10 ml) with $HSCH_2CO_2Me$ (100 µl; 1.1 mmol) and $K_2CO_3$ (0.28 g) and work-up as described above gave compound **21** (0.26 g, 53%) as a pale yellow gum; $\delta_H$7.00-7.45 (4H, m), 5.47 (1H,s), 4.11 (2H, q, J = 8Hz), 4.03 (2H, AB), 3.76 (3H, s), 3.61 (3H, s), 3.32 (2H, s), 2.35 (3H, s) and 1.18 (3H, t, J = 7Hz).

2-(Benzylthiomethyl)-4-(2,3-dichlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine **22**. Reaction of $SO_2Cl_2$ (0.52 ml; 6.5 mmol) in DMF (10 ml) with **7** (1.30 g, 3.25 mmol) and imidazole (0.55 g, 10.2 mmol) in DMF (20 ml) and work-up as described above afforded crude **14**. Reaction of a solution of **14** in THF (10 ml) with $PhCH_2SH$ (1.0 ml; 8.05 mmol) and $K_2CO_3$ (1.3 g) in THF (10 ml) and DMF (10 ml) and work-up as described above gave compound **22** (650 mg, 39%) as a yellow gum which was characterised as a monohydrate (Found: C, 57.5; H, 5.0; N, 2.6. $C_{25}H_{25}Cl_2NO_4S.H_2O$ requires: C, 57.3; H, 5.2; N, 2.7); $\delta_H$ 7.20-7.45 (7H, m), 7.08 (1H, t, J = 8Hz), 6.61 (1H, s), 5.49, (1H, s), 3.83-4.18 (4H, m), 3.70 (2H, s), 3.62 (3H, s), 2.24 (3H, s) and 1.19 (3H, t, J = 7Hz).

4-(2,3-Dichlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl)-6-methyl-2-(2-pyridyl)methoxymethyl-1,4-dihydropyridine **23**. Reaction of $SO_2Cl_2$ (0.27 g, 2.0 mmol) in DMF (10 ml) with **7** (0.40 g, 1.0 mmol) and imidazole (0.68 g, 10 mmol) in DMF (5 ml) and work-up as described above afforded crude **14**. Reaction of a solution of **14** in THF (5 ml) with a mixture of pyridine-2-methanol (0.24 g, 2.0 mmol) and NaH (0.15 g, 5 mmol; 80% dispersion in oil) in THF (5 ml) and work-up as described above gave, after crystallisation of the residue from $Et_2O$, compound **23** (100 mg, 20%) as colourless crystals, m.p. 156-157°C, which were characterised as a hemihydrate (Found: C, 58.6; H, 4.9; N, 5.7. $C_{25}H_{24}Cl_2N_2O_5.0.5H_2O$ requires: C, 58.6; H, 4.9; N, 5.5); $\delta_H$ 8.66 (2H, d, J = 6Hz), 8.47 (1H, s), 7.79 (1H, dt, J = 6 and 2Hz), 7.24-7.42 (5H, m), 7.10 (1H, t, J = 8Hz), 5.52 (1H, s), 4.93 (2H, AB), 4.76 (2H, AB), 4.07 (2H, q, J = 7Hz), 3.63 (3H, s), 2.45 (3H, s) and 1.21 (3H, q, J = 7Hz).

2-(2-Aminoethylthiomethyl)-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine 24. Reaction of $SO_2Cl_2$ (1.08 g, 8 mmol) in DMF (10 ml) with 13 (1.45 g, 4.0 mmol) and imidazole (1.36 g, 20 mmol) in DMF (20 ml) and work-up as described above afforded crude 18. Reaction of a solution of 18 in THF (10 ml) with $HSCH_2CH_2NH_2$ HCl (1.13 g, 10 mmol) and $K_2CO_3$ (1.38 g) in THF (20 ml) and work-up as described above gave, after crystallisation of the residue from $Et_2O$, compound 24 as a pale yellow solid, m.p. 116-119°C (Found: C, 56.7; H, 6.2; N, 6.4. $C_{20}H_{25}ClN_2O_4S$ requires: C, 56.5; H, 5.9; N, 6.6); $\delta_H$ 7.00-7.45 (5H, m), 5.46 (1H, s) 4.04-4.20 (2H, m), 4.05 (2H, s), 3.62 (3H, s), 2.97 (2H, t, J = 7Hz), 2.64 (2H, t, J = 7Hz), 2.38 (3H, s), 1.65 (2H, s) and 1.23 (3H, t, J = 7Hz).

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