A Novel, Base-induced Fragmentation of Hantzsch-type 4-Aryl-1,4-dihydropyridines

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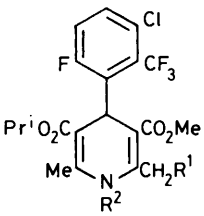
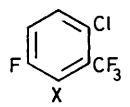
Hantzsch-type 1,4-dihydropyridine derivatives substituted with highly electron-deficient aryl groups in the 4-position, on treatment with a variety of basic reagents in non-hydroxylic solvents, undergo an unexpected and ready scission of the inter-ring bond to give the corresponding 4-unsubstituted pyridine and an arene derived from the original 4-substituent. The scope of the reaction has been investigated and possible mechanisms are discussed.

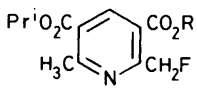
The 4-aryl-1,4-dihydropyridine derivatives obtained from the Hantzsch synthesis[1] have attracted considerable attention in recent years, largely on account of their ability to influence the movement of calcium ions across the membranes of cardiac and vascular smooth muscle cells *via* voltage-dependent channels.[2] In particular, a number of compounds which inhibit this process (the so-called calcium antagonists or calcium channel blockers) have proved valuable as drugs for the treatment of cardiovascular disorders.[3] Our own investigations in this area led to the development of a series of calcium antagonists, typified by compound (**1**),[4] the unusual selectivity profile of which made them the subject of extended pharmacological investigations. Compounds such as (**1**) differ structurally from earlier dihydropyridine calcium antagonists in having a polysubstituted, highly electron-deficient 4-aryl substituent combined with a fluoromethyl group in the 2-position. We now report a novel fragmentation reaction of dihydropyridines of this type which was first observed during studies into the reactivity of the fluoromethyl substituent towards nucleophiles.



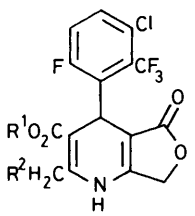
(**1**) R^1 = F, R^2 = H
(**2**) R^1 = OH, R^2 = H
(**5**) R^1 = F, R^2 = Me



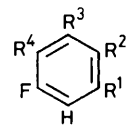
(**3**) X = H



(**4**) R = Me
(**29**) R = H



(**6**) R^1 = Pr^i, R^2 = H
(**36**) R^1 = Me, R^2 = F



(**28**) **a**; R^1 = CF_3, R^2 = R^3 = R^4 = H
b; R^1 = SO_2Ph, R^2 = F, R^3 = R^4 = H
c; R^1 = R^2 = R^4 = F, R^3 = H
d; R^1 = CF_3, R^2 = F, R^3 = R^4 = H
e; R^1 = R^2 = R^3 = R^4 = F
f; R^1 = CF_3, R^2 = R^4 = Cl, R^3 = H

Results and Discussion

Although the fluoromethyl derivative (**1**) is quite readily hydrolysed to the hydroxymethyl compound (**2**) in aqueous solvent mixtures,[5] it is remarkably stable towards substitution by a variety of other nucleophiles.[6] It was surprising, therefore, that (**1**) reacted rapidly and cleanly on treatment with sodium or tetraethylammonium cyanide in dry dimethylformamide (DMF) (60 °C, 15 min; or 20 °C, 16 h) to give products which, significantly, lacked the intense fluorescence under u.v. light which is characteristic of (**1**) and its analogues. The mixture produced could be readily separated into two components: a volatile liquid identical with the known[4] 2-chloro-5-fluorobenzylidyne trifluoride (**3**) and a crystalline material identified as the 4-unsubstituted pyridine derivative (**4**). Recoveries of both products were excellent. The reaction requires only catalytic quantities of the cyanide reagent (5—10 mol%).

Because this process did not appear to be general for nucleophilic agents we felt that the cleavage reaction might be a result of the basic rather than the nucleophilic properties of the reaction medium, a hypothesis supported by the observation that the *N*-methyl analogue (**5**)[7] did not undergo this reaction. Other basic reaction media were investigated, and the same reaction was observed with a variety of other bases and non-hydroxylic solvents (Table 1). No reaction was observed, however, with tetraethylammonium cyanide in chloroform (65 °C, 24 h) or with sodium cyanide or sodium ethoxide in ethanol (80 °C, 24 h), while sodium hydroxide in aqueous solvent mixtures (100 °C, 36 h) gave only the lactone (**6**).[5] The reaction of (**1**) with sodium cyanide in DMF was not significantly affected by the addition of radical initiators or inhibitors, or by passage of oxygen or nitrogen through the mixture.

In most cases the cleavage reaction was clean and essentially quantitative; however when hydroxide or methoxide was used as the base, ester hydrolysis and exchange reactions of initially formed (**4**) led to the detection of the esters (**29**) and (**30**), respectively, as minor by-products.

In order to elucidate the mechanism and scope of this novel reaction, the effect of varying the substituents about the dihydropyridine ring has been examined. Although we have not carried out detailed kinetic analyses, some useful qualitative deductions can be made, based on the reaction temperatures and times required.

Apart from the previously mentioned effect of *N*-substitution, the most important determinant of reaction appears to be the nature of the 4-aryl substituent. Table 2 shows the results of reactions of a series of analogues of (**1**), prepared previously as part of our medicinal chemical investigations, which differ solely in the nature of their 4-substituent. In each case where reaction occurred (**4**) was the only pyridine product and could be isolated in high yield (70—90%). Because of difficulties of handling the rather volatile arene derivatives derived from the 4-aryl substituent, we did not attempt to characterise them in every case; however compounds (**28a—f**) were identified as the products of the reactions of (**19**), (**21**), (**22**), (**23**), (**24**), and (**27**) respectively, by spectral or gas chromatographic comparison with authentic materials. With the exception of the reaction of (**24**), where a small amount of yellow polymer was also formed, no other products were observed in any of the reactions in Table 2.

These results give rise to the following observations. (i) The minimum requirement for the cleavage reaction is a 4-aryl substituent substituted in both *ortho*-positions by inductively electron-withdrawing groups (*e.g.* F, Cl, OMe, NO_2, CF_3, C_2F_5, and SO_2Ph). (ii) Substitution by additional electron-withdrawing groups in the *meta*-positions produces a significant increase in the rate of cleavage [*e.g.* (**14**) *vs.* (**17**) *vs.* (**18**) *vs.* (**22**), and (**19**) *vs.* (**1**) *vs.* (**27**)]. (iii) Substitution by F in the *para*-position [*e.g.* (**16**) *vs.* (**14**) and (**24**) *vs.* (**22**)] produces only a marginal rate enhancement. (iv) Increased steric bulk in the *ortho*-positions of the 4-substituent is rate-enhancing [*e.g.* (**20**) *vs.* (**19**) *vs.* (**14**); (**21**) and (**23**) *vs.* (**18**)].

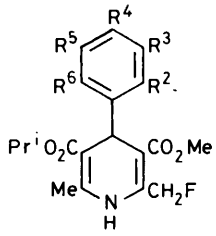
In contrast to the effects of the 4-substituent, substituents in positions 2, 3, 5, and 6 of the dihydropyridine have relatively little effect on the rate of the cleavage reaction, provided that they are themselves unaffected by the reaction conditions. Thus the 2,6-dimethyl compound (**31a**) reacts at the same rate as (**1**) with sodium cyanide in DMF, whilst the 2,6-bis(trifluoromethyl) compound (**32**) [prepared by dehydration of the piperidinediol (**43**) obtained from the attempted Hantzsch synthesis using

Table 1. Effect of base and solvent on the rate of cleavage of the dihydropyridine (1) to products (**3**) and (**4**)

Base	Solvent	Temp. (°C)	Time (min)
NaCN	DMF[a]	60	15
Et_4NCN	DMF	60	15
Et_4NCN	THF[a]	60	60
Et_4NCN	MeCN	60	30
NaCN	Me_2SO	60	15
NaCN	Me_2CO	55	40
Et_4NCN	EtOAc	75	10
Et_4NCN	PhH	80	40
Et_4NCN	1,4-Dioxane	95	25
DBU[a]	THF	60	20
NaOH	Me_2SO	25	75[b]
NaH	DMF	20	60
NaOMe	DMF	60	15[c]
KF	DMF	75	20

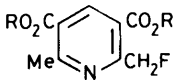
[a] DMF = Dimethylformamide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, THF = tetrahydrofuran. [b] A small amount of acid (**29**) is formed as a by-product by subsequent hydrolysis of (**4**) (by ^1H n.m.r. and g.l.c.–mass spectrometry). [c] Small amounts of ester exchange products (**30a** and **b**) are also formed as by-products from (**4**) (by g.l.c.–mass spectrometry).

Table 2. Reactions of dihydropyridines (**7**)—(**27**) with CN^- in DMF



	R^2	R^3	R^4	R^5	R^6	Temp. (°C)	Time (min)	Products[a]
(**7**)	NO_2	H	H	H	H	140	N.r.[b]	
(**8**)	H	H	NO_2	H	H	140	N.r.	
(**9**)	CF_3	H	H	H	H	140	N.r.	
(**10**)	Cl	Cl	H	H	H	140	N.r.	
(**11**)	OMe	OMe	H	H	H	140	N.r.	
(**12**)	F	H	H	H	Me	140	N.r.	
(**13**)	F	H	CF_3	Cl	H	140	N.r.	
(**14**)	F	H	H	H	F	140	180	(**14**) (70%)[c] + (**4**) (30%)[c]
(**15**)	Cl	H	H	H	Cl	140	180	(**15**) (50%)[c] + (**4**) (50%)[c]
(**16**)	F	H	F	H	F	140	180	(**4**)
(**17**)	F	NO_2	H	H	F	120	60	(**4**)
(**18**)	F	F	H	H	F	120	20	(**4**)
(**19**)	F	H	H	H	CF_3	100	60	(**4**) + (**28a**)[d]
(**20**)	F	H	H	H	C_2F_5	100	5[e]	(**4**)
(**21**)	SO_2Ph	F	H	H	F	75	20	(**4**) + (**28b**)[d]
(**22**)	F	F	H	F	F	60	60	(**4**) + (**28c**)[d]
(**23**)	CF_3	F	H	H	F	60	40	(**4**) + (**28d**)[d]
(**1**)	CF_3	Cl	H	H	F	60	20	(**3**) + (**4**)
(**24**)	F	F	F	F	F	60	15	(**4**) + (**28e**)[d]
(**25**)	NO_2	Cl	H	H	F	60	15	(**4**)
(**26**)	CF_3	Cl	H	H	OMe	60	8	(**4**)
(**27**)	CF_3	Cl	H	Cl	F	60	2	(**4**) + (**28f**)[d]

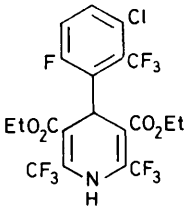
[a] Isolated products except where otherwise stated. [b] N.r. = no detectable reaction after 3 h. [c] Composition of mixture estimated by ^1H n.m.r. after 3 h. [d] Identified by ^1H n.m.r. and g.l.c.–mass spectrometry. [e] Slow reaction (> 3 h) also at 60 °C.



(30)

a; R = Me

b; R = Pr



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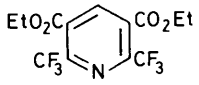

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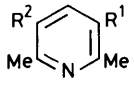


(35)

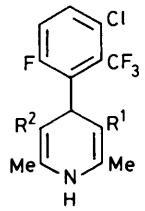
a; R^1 = CO_2Me, R^2 = CO_2Pr^i

b; R^1 = R^2 = CO_2Me

c; R^1 = R^2 = CO_2Et

d; R^1 = R^2 = CO_2Pr^i

e; R^1 = R^2 = CN



(31)

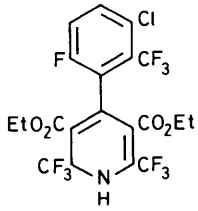
a; R^1 = CO_2Me, R^2 = CO_2Pr^i

b; R^1 = R^2 = CO_2Me

c; R^1 = R^2 = CO_2Et

d; R^1 = R^2 = CO_2Pr^i

e; R^1 = R^2 = CN



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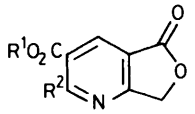
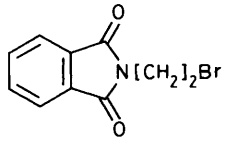


(37) R^1 = Pr^i, R^2 = Me

(38) R^1 = Me, R^2 = CH_2F



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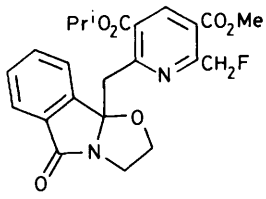

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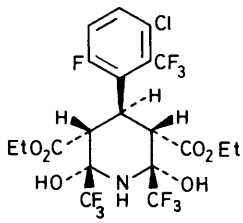

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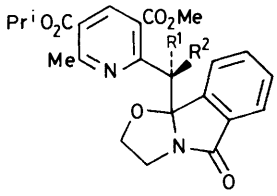
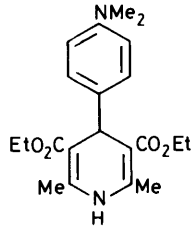


(40)

a; R^1 = H, R^2 = F

b; R^1 = F, R^2 = H



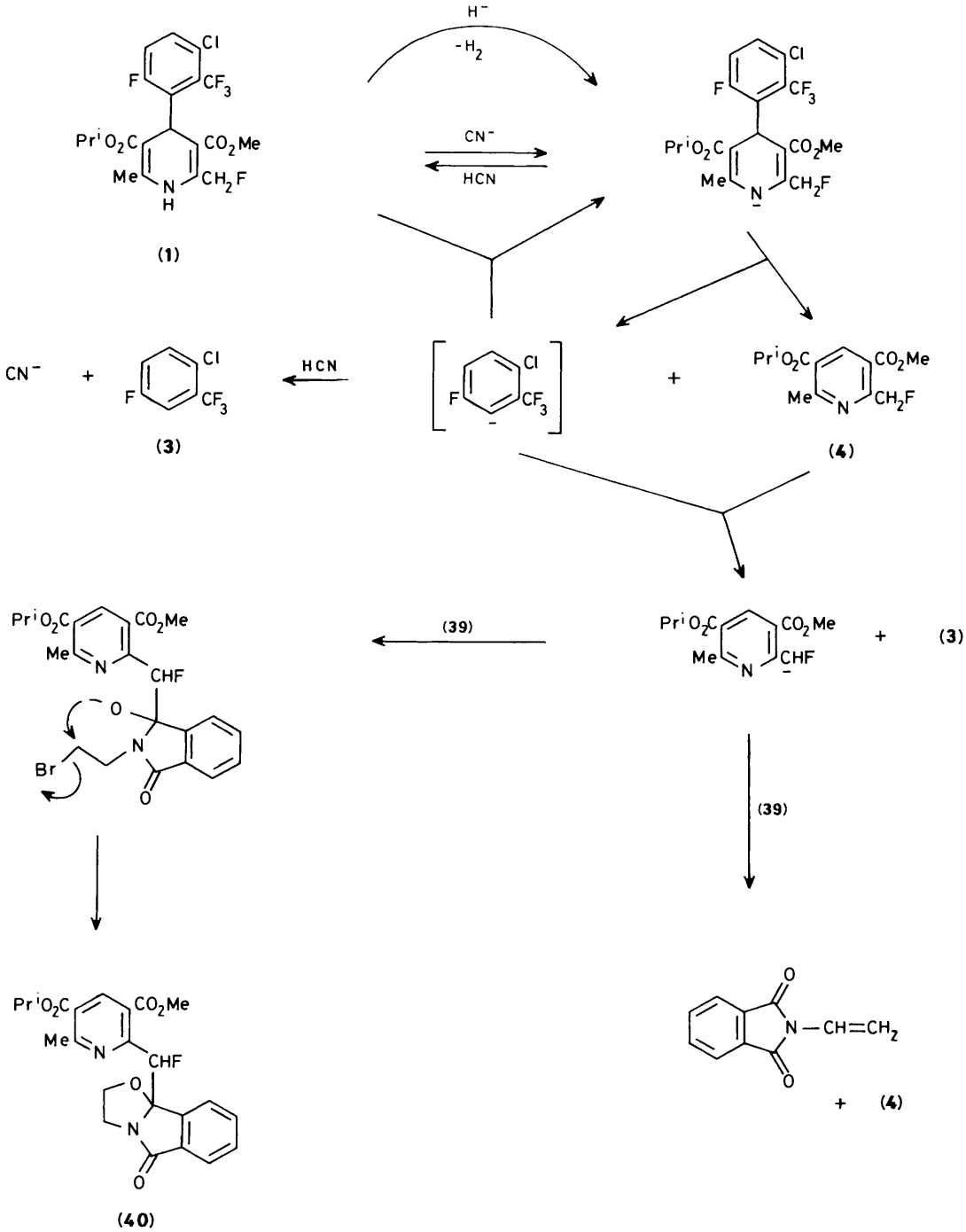
(42)

ethyl 4,4,4-trifluoroacetoacetate and the appropriate aldehyde] reacts at the same rate as (**1**) with tetraethylammonium cyanide or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF, giving the oily pyridine (**34**). Compound (**32**) is remarkable in that it reacts with bases in DMF to give, in addition to a small amount of cleavage product, substantial amounts of a higher melting isomer of (**32**). We have assigned to this isomer the 1,2-dihydro structure (**33**) on the basis of its spectral properties. This difference in reactivity is presumably a reflection of the enhanced relative acidity of the dihydropyridine 4-proton resulting from the combined electron withdrawal of the two CF_3 substituents; the reasons why this isomerisation occurs only in DMF are not entirely clear, however.

Changing the esters has similarly little effect on the rate of reaction in a given series. Thus, for example, compounds (**31a**—**e**) are all cleaved to the corresponding pyridines (**35a**—**e**) by sodium cyanide in DMF at 60 °C (20—45 min). Incorporating the esters in a lactone ring, however, as in (**6**) and (**36**), significantly reduces the rate of cleavage; both lactones require 1 h at 100 °C, to produce (**37**) and (**38**), respectively. Models suggest that lactone formation leads to a considerable reduction in the steric interaction between the ester oxygen atoms and the *ortho*-substituents in the 4-aryl ring; hence this rate reduction is probably related to that previously observed on reduction of the size of the 4-aryl *ortho*-substituents.

Mechanism and Conclusions

The failure of the reaction with the *N*-methyl derivative (**5**), together with the observation that (**1**) can be cleaved by an excess of sodium deuteroxide in [$^2H_6$]dimethyl sulphoxide to give monodeuterio-(**3**) and (**4**) lacking any detectable incorporation of label (by ^1H n.m.r.), suggests that the reaction is initiated by abstraction of the 1,4-dihydropyridine 1-proton by the base. The driving force for the subsequent carbon–carbon bond cleavage is presumably the relief of the considerable steric interaction between the 4-substituent and the flanking 3- and 5-substituents, together with the formation of an aromatic pyridine. The requirements for the 4-aryl substituent, specifically substitution, particularly in the *ortho*-positions, by powerful inductively electron-withdrawing substituents, suggest that this group may be leaving as a formal aryl anion; the substituent effects are reminiscent of those for kinetic acidity of aromatic protons which involves similar anion formation.[8] Attempts to trap this anion have so far failed, rapid protonation always being favoured. When the reaction is performed under conditions of reversible deprotonation (*e.g.* NaCN, KF, or DBU) the required proton source is presumably either the protonated base or the starting dihydropyridine. Under irreversible deprotonation conditions (*e.g.* NaH) neither of these sources is available and experiments using added electrophiles suggest that the relatively acidic protons of the 2- and 6-alkyl substituents of the product (**4**) may react under these circumstances. Thus, for example, reaction of (**1**) with sodium hydride in DMF at 20 °C in the presence of *N*-(2-bromoethyl)phthalimide (**39**) gave, in addition to (**3**) and (**4**), four other products identified as *N*-vinylphthalimide, the two diastereoisomeric compounds (**40a** and **b**) in almost equal amounts (total yield 18%), and a small amount (4%) of a third isomer (**41**). These somewhat unusual tricyclic lactam structures were deduced from the absence of further interproton coupling for the pyridine CHF and CH_2 protons of (**40a** and **b**) and (**41**), respectively. Analogous products have been observed in



Scheme.

reactions of (**39**) with lithium acetylides,[9] ester enolates,[10] and aryl-lithiums.[11]

We therefore currently favour the mechanism shown in the Scheme as that most consistent with the experimental observations.

The aromatisation of Hantzsch 1,4-dihydropyridines with concomitant elimination of a 4-substituent (other than hydrogen) has been observed previously under conditions of one-[12] or two-[13] electron oxidation. In these cases the substituent eliminated was always aliphatic and was lost as a stabilised alkyl (or aralkyl) radical or cation, respectively. There is also an example[14] of loss of the highly electron-rich *p*-(dimethylamino)phenyl substituent from the 1,4-dihydropyridine (**42**) by the action of oxidising agents, a reaction probably initiated by electrophilic attack on the 4-substituent. To our knowledge the reaction we have described is the first example of aromatisation of Hantzsch-type 1,4-dihydropyridines with elimination of a 4-substituent which occurs under mild, basic, non-oxidative conditions and also the first reasonably general reaction of this type to involve cleavage of a pyridyl–aryl bond as a key step.

The extreme ease with which this reaction takes place, combined with the fact that it is favoured by those substituents which are also associated with enhanced biological activity,[2] is

of particular significance in connection with the synthesis of dihydropyridines and their possible fate *in vivo*. The extremely clean and essentially quantitative nature of the cleavage suggests also that it may provide a viable alternative synthesis of 4-unsubstituted pyridines, particularly those bearing other substituents which would preclude the use of harsh, oxidising conditions.

Experimental

M.p.s were obtained on Büchi oil-bath apparatus. Mass spectra were obtained with a Kratos MS30 or MS50 instrument. N.m.r. spectra were determined with a Bruker AM360 spectrometer for solutions in $CDCl_3$ unless otherwise stated; chemical shifts are reported in p.p.m. relative to tetramethylsilane for ^1H and ^{13}C spectra, and to $CFCl_3$ for ^{19}F spectra. U.v. spectra were recorded with a Perkin-Elmer 552S spectrometer for solutions in ethanol. I.r. spectra were obtained with a Perkin-Elmer 297 or Pye-Unicam PU 9514 spectrometer for potassium bromide discs. Elemental analyses were carried out by the Physical Chemistry Department of Fison's Pharmaceutical Division, R and D Laboratories. Column chromatography was carried out under nitrogen on Merck Kieselgel 60 (230—400 mesh). T.l.c. was carried out on pre-coated silica gel plates (Merck Kieselgel $60F_{254}$, 250 μm thickness). Solvents were dried by conventional procedues.[15] Light petroleum used was the fraction of b.p. 60—80 °C unless otherwise stated.

1,4-*Dihydropyridines*.*—The preparation of most of the compounds used in this study has been described previously.[4,5,7,16] The following compounds, however, have not been reported elsewhere.

3-*Methyl* 5-(1-*methylethyl*) 2-(*fluoromethyl*)-1,4-*dihydro*-6-*methyl*-4-(4-*nitrophenyl*)*pyridine*-3,5-*dicarboxylate* (**8**). A solution of 4-nitrobenzaldehyde (5.0 g, 33 mmol), methyl 4-fluoro-3-oxobutanoate[4] (4.43 g, 33 mmol),* and (1-methylethyl) 3-aminobut-2-enoate[17] (4.7 g, 33 mmol) in dry t-butyl alcohol (50 ml) was heated at 60 °C with stirring and under nitrogen for 72 h. The solution was cooled and the solvent removed under reduced pressure. The oily residue was purified by column chromatography [dichloromethane–ethyl acetate (20:1) as eluant] to give *compound* (**8**) (7.13 g, 55%) as yellow needles, m.p. 127 °C (from ethanol) (Found: C, 57.8; H, 5.5; N, 7.05; F, 4.9. $C_{19}H_{21}FN_2O_6$ requires C, 58.2; H, 5.4; N, 7.1; F, 4.8%); $\nu_{max.}$ 3 200 (N–H), 1 690 (C=O), 1 480 (NO_2), and 1 350 cm^{-1} (NO_2); $\lambda_{max.}$ 364 (log ε 3.66), 276 (4.09), and 230 nm (4.24); δ_H 1.09 (3 H, d, *J* 6 Hz, CH_3CH), 1.24 (3 H, d, *J* 6 Hz, CH_3CH), 2.40 (3 H, s, 6-CH_3), 3.64 (3 H, s, CO_2CH_3), 4.95 [1 H, m, $(CH_3)_2CH$], 5.06 (1 H, s, dihydropyridine 4-H), 5.52—5.70 (2 H, AB part of ABX, J_{HH} 15, J_{HF} 45 Hz, CH_2F), 6.60 (1 H, br d, J_{HF} 6.5 Hz, NH), 7.43 (2 H, d, aryl 2- and 6-H), and 8.10 (2 H, d, aryl 3- and 5-H); *m/z* 392 (M^+), 361, 333, and 270 (base).

3-*Methyl* 5-(1-*methylethyl*) 2-(*fluoromethyl*)-4-(2-*fluoro*-6-*methylphenyl*)-1,4-*dihydro*-6-*methylpyridine*-3,5-*dicarboxylate* (**12**). 2-Fluoro-6-methylbenzaldehyde (1.9 g, 14 mmol), methyl 4-fluoro-3-oxobutanoate* (1.87 g, 14 mmol) and (1-methylethyl) 3-aminobut-2-enoate (2.0 g, 14 mmol) in dry t-butyl alcohol (30 ml) were stirred at 60 °C for 96 h. The solution was cooled, trifluoroacetic acid (0.6 ml, 0.88 g, 7.7 mmol) was added, and the solution was stirred at 20 °C for 1 h and then concentrated under reduced pressure. The remaining brown oil was separated by column chromatography on silica [dichloromethane–ethyl acetate (1%) as eluant]. The fractions containing fluorescent material were combined to afford *compound* (**12**) as a pale yellow powder (0.36 g, 7%), m.p. 132—134 °C after trituration with light petroleum (Found: C, 63.3; H, 6.1; F, 9.7; N, 3.6. $C_{20}H_{23}F_2NO_4$ requires C, 63.3; H, 6.1; F, 10.0; N, 3.7%); $\lambda_{max.}$ 360 (log ε 3.85) and 231 nm (4.25); $\nu_{max.}$ 3 350 (NH), 1 680 (C=O), and 1 650 cm^{-1} (C=O); δ_H 1.03 (3 H, d, *J* 7 Hz, CH_3CH), 1.21 (3 H, d, *J* 7 Hz, CH_3CH), 2.30 (3 H, s, 6-CH_3), 2.56 (3 H, s, $ArCH_3$), 3.57 (3 H, s, CO_2CH_3), 4.95 (1 H, m, Me_2CH), 5.39 (1 H, s, dihydropyridine 4-H), 5.48—5.67 (2 H, AB part of ABX, CH_2F), 6.60 (1 H, br d, NH), and 6.8—7.0 (3 H, m, aryl); *m/z* 379 (M^+), 359, 348, 337, 320, and 270 (base).

3-*Methyl* 5-(1-*methylethyl*) 4-[5-*chloro*-2-*fluoro*-4-(*trifluoromethyl*)*phenyl*]-2-(*fluoromethyl*)-1,4-*dihydro*-6-*methylpyridine*-3,5-*dicarboxylate* (**13**). This was prepared as described for compound (**8**) from 5-chloro-2-fluoro-3-(trifluoromethyl)-benzaldehyde[4] (1.68 g, 7.4 mmol) and appropriate molar equivalents of the other reagents. *Compound* (**13**) was obtained as yellow crystals (0.7 g, 21%), m.p. 125—127 °C (from light petroleum–propan-2-ol) (Found: C, 51.4; H, 4.1; Cl, 7.6; N, 2.9. $C_{20}H_{20}ClF_4NO_4$ requires C, 51.3; H, 4.1; Cl, 7.6; N, 3.0%); $\lambda_{max.}$ 362 (log ε 3.77), 274 (3.61), and 232 nm (4.35); $\nu_{max.}$ 3 430 (NH) and 1 700 cm^{-1} (C=O); δ_H 1.06 (3 H, d, *J* 6 Hz, CH_3CH), 1.26 (3 H, d, *J* 6 Hz, CH_3CH), 2.33 (3 H, s, 6-CH_3), 3.62 (3 H, s, CO_2CH_3), 4.95 [1 H, m, $(CH_3)_2CH$], 5.22 (1 H, s, dihydropyridine 4-H), 5.51—5.74 (2 H, m, AB part of ABX, CH_2F), 6.62 (1 H, br d, NH), 7.27 (1 H, d, J_{HF} 10 Hz, aryl 6-H), and 7.39 (1 H, d, J_{HF} 6 Hz, aryl 3-H); *m/z* 467 (^{35}Cl, M^+), 424, 380, and 270 (base).

3-*Methyl* 5-(1-*methylethyl*) 4-(2,6-*dichlorophenyl*)-2-(*fluoromethyl*)-1,4-*dihydro*-6-*methylpyridine*-3,5-*dicarboxylate* (**15**). A solution of 2,6-dichlorobenzaldehyde (2.83 g, 16.2 mmol), methyl 4-fluoro-3-oxobutanoate* (2.20 g, 16.2 mmol), piperidine (0.2 ml), and hexanoic acid (0.3 ml) in benzene (100 ml) was stirred at 20 °C for 48 h. The solution was concentrated to a pale brown oil which was purified by column chromatography [light petroleum–ethyl acetate (7%) as eluant] to give an *E*/*Z* mixture of benzylidene acetoacetates (3.75 g, 77%) as a pale yellow oil, which was used without purification. This oil and (1-methylethyl) 3-aminobut-2-enoate (1.78 g, 12.5 mmol) in dry t-butyl alcohol (30 ml) were heated at 80 °C for 5 days. The cooled solution was concentrated under reduced pressure and the residue purified by column chromatography using dichloromethane as eluant to give *compound* (**15**) (1.7 g, 33%) as yellow crystals, m.p. 125—127 °C (from light petroleum) (Found: C, 55.1; H, 5.0; Cl, 17.3; N, 3.3. $C_{19}H_{20}Cl_2FNO_4$ requires C, 54.8; H, 4.8; Cl, 17.0; N, 3.4%); $\nu_{max.}$ 3 340 (NH) and 1 690 cm^{-1} (C=O); $\lambda_{max.}$ 367 (log ε 3.81) and 220 nm (4.33); δ_H 0.83 (3 H, d, *J* 6 Hz, CH_3CH), 1.22 (3 H, d, *J* 6 Hz, CH_3CH), 2.28 (3 H, s, 6-CH_3), 3.53 (3 H, s, CO_2CH_3), 5.00 (1 H, m, Me_2CH), 5.90 (1 H, s, dihydropyridine 4-H), 6.95 (1 H, br d, NH), and 7.2—7.5 (3 H, m, aryl); *m/z* 415 ($^{35}Cl_2$, M^+), 395, 372, and 270 (base).

4-[3-*Chloro*-6-*fluoro*-2-(*trifluoromethyl*)*phenyl*]-1,4-*dihydro*-2,6-*dimethylpyridine*-3,5-*dicarbonitrile* (**31e**). A solution of 3-chloro-6-fluoro-(2-trifluoromethyl)benzaldehyde (5 g, 22 mmol) and 3-aminobut-2-enenitrile (3.62 g, 44 mmol) in ethanol (100 ml) was heated at reflux for 40 h. The solution was cooled and trifluoroacetic acid (5 ml) added. The resulting suspension was kept at 0—5 °C for 1 h and the pale yellow precipitate filtered off and recrystallised from ethanol to give *compound* (**31e**) (2.3 g, 29%), m.p. 253 °C (Found: C, 53.7; H, 3.0; Cl, 9.7; F, 21.4; N, 11.6. $C_{16}H_{10}ClF_4N_3$ requires C, 54.0; H, 2.8; Cl, 10.0; F, 21.4; N, 11.8%); $\nu_{max.}$ 3 300 (N–H) and 2 200 cm^{-1} (C≡N); $\lambda_{max.}$ 354 (log ε 3.72), 286 (3.76), and 278 nm (3.81); δ_H[$(CD_3)_2SO$] 2.00 (6 H, s, 2 × CH_3), 5.00 (1 H, q, J_{HF} 4.5 Hz, dihydropyridine 4-H), 7.72

* **CAUTION**: Studies in our toxicology department have indicated that methyl 4-fluoro-3-oxobutanoate (and presumably other esters of this acid) is very readily absorbed through the skin to produce extremely severe toxic effects. *It has been estimated that skin contact with as little as* 1 g *of undiluted material could prove fatal in humans.* We urge, therefore, that every precaution be taken to avoid the possibility of accidental contact with this substance or with solutions or reaction mixtures which may contain it.

(1 H, dd, J_{HH} 8.8 Hz, J_{HF} 11 Hz, aryl 5-H), 7.83 (1 H, dd, J_{HH} 8.8, J_{HF} 4.8 Hz, aryl 4-H), and 9.70 (1 H, br s, NH); *m/z* 355 (^{35}Cl, M^+) and 158 (100).

Diethyl 4-[3-*chloro*-6-*fluoro*-2-(*trifluoromethyl*)*phenyl*]-1,4-*dihydro*-2,6-*bis*(*trifluoromethyl*)*pyridine*-3,5-*dicarboxylate* (**32**). A solution of 3-chloro-6-fluoro-2-(trifluoromethyl)benzaldehyde (5.0 g, 22 mmol), ethyl 4,4,4-trifluoro-3-oxobutanoate (8.1 g, 44 mmol), and ammonium acetate (1.7 g, 22 mmol) in dry t-butyl alcohol (40 ml) was heated at 60 °C for 24 h, cooled, and concentrated under reduced pressure to give an oil. Trituration with light petroleum gave *diethyl* t-4-[3-*chloro*-6-*fluoro*-2-(*trifluoromethyl*)*phenyl*]-c-2,c-6-*dihydroxy*-t-2,t-6-*bis*(*trifluoromethyl*)*piperidine*-r-3,c-5-*dicarboxylate* (**43**) (4.1 g, 33%), m.p. 123—125 °C (Found: C, 40.2; H, 3.0; Cl, 6.05; F, 32.5; N, 2.2. $C_{20}H_{18}ClF_{10}NO_6$ requires C, 40.45; H, 3.05; Cl, 6.0; F, 32.0; N, 2.35%); $\nu_{max.}$ 3 600—3 200 (OH), 3 360 (N–H), and 1 710 cm^{-1} (C=O); $\lambda_{max.}$ 285 (log ε 3.40) and 278 nm (3.39); δ_H 0.85 (6 H, t, *J* 7 Hz, CH_3CH_2), 3.28 (1 H, br s, NH), 3.65 (2 H, d, *J* 12 Hz, piperidine 3- and 5-H), 3.90 (4 H, m, CH_2CH_3), 4.80 (1 H, complex m, piperidine 4-H), 5.63 (2 H, br s, OH), 7.26 (1 H, dd, J_{HH} 9, J_{HF} 11 Hz, aryl 5-H), and 7.56 (1 H, dd, J_{HH} 9, J_{HF} 5 Hz, aryl 4-H) [nuclear Overhauser difference measurement shows mutual enhancement between signals at δ 4.80 (piperidine 4-H) and 5.63 (2 × OH)]; *m/z* 576 (^{35}Cl, M^+ − OH) 530, 524, 506, and 297 (base).

The dihydroxy-compound (**43**) (3.8 g, 6.4 mmol) in dichloromethane (100 ml) was added dropwise with vigorous stirring to concentrated sulphuric acid (100 ml) and dichloromethane (100 ml) cooled to 4 °C in ice–salt. When the addition was complete, stirring was continued for 20 min and the two-phase mixture was then poured slowly onto ice–water. The organic phase was separated, washed with saturated brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica [light petroleum–dichloromethane (3:2)]. The oil obtained, dissolved in light petroleum (20 ml), was kept at −20 °C for 72 h. The crystals produced were collected, affording *compound* (**32**) (2.1 g, 59%), m.p. 55—57 °C (Found: C, 43.0 H, 2.6; Cl, 6.4; F, 34.0; N, 2.5. $C_{20}H_{14}ClF_{10}NO_4$ requires C, 43.1; H, 2.5; Cl, 6.4; F, 34.1; N, 2.5%); $\nu_{max.}$ 3 380 (N–H) and 1 720 cm^{-1} (C=O); $\lambda_{max.}$ 344 (log ε 3.53), 290 (3.72), and 284 nm (3.70); δ_H 1.16 (6 H, t, CH_3CH_2), 4.10 (4 H, m, CH_3CH_2), 5.98 (1 H, m, dihydropyridine 4-H), 6.42 (1 H, br s, NH), 7.22 (1 H, dd, J_{HH} 9, J_{HF} 11 Hz, aryl 5-H), and 7.47 (1 H, d, J_{HH} 9, J_{HF} 5 Hz, aryl 4-H); δ_F −54.7 (3 F, d, $ArCF_3$), −65.2 (6 F, s, dihydropropyridine 2- and 6-CF_3), and −112.0 (1 F, dd, ArF); *m/z* 557 (^{35}Cl, M^+), 528, 512, and 360 (base).

Methyl 4-[3-*chloro*-6-*fluoro*-2-(*trifluoromethyl*)*phenyl*]-2-(*fluoromethyl*)-1,4,5,7-*tetrahydro*-5-*oxofuro*[3,4-b]*pyridine*-3-*carboxylate* (**36**). A solution of 5-methyl 3-(1-methylethyl) 2-(bromomethyl)-4-[3-chloro-6-fluoro-2-(trifluoromethyl)-phenyl]-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate[16] (0.5 g, 0.9 mmol) in chloroform (10 ml) was heated at reflux for 4 h. The crystals which separated on cooling were collected, washed with cold chloroform, and dried to give the *lactone* (**36**) (0.2 g, 52%), m.p. 216—218 °C (decomp.) (Found: C, 48.2; H, 2.8; Cl, 8.3; F, 22.25; N, 3.1. $C_{17}H_{11}ClF_5NO_4$ requires C, 48.2; H, 2.6; Cl, 8.4; F, 22.4; N, 3.3%); $\lambda_{max.}$ 353 (log ε 3.86) and 280 nm (3.75); $\nu_{max.}$ 3 250 (NH), 1 735 (C=O), 1 705 (C=O), and 1 680 cm^{-1} (C=O); δ_H[$(CD_3)_2SO$] 3.44 (3 H, s, OCH_3), 4.84 (2 H, s, OCH_2), 5.61 (2 H, d, J_{HF} 48 Hz, CH_2F), 5.71 (1 H, q, dihydropyridine 4-H), 7.51 (1 H, dd, aryl 5-H), 7.69 (1 H, dd, aryl 4-H), and 10.20 (1 H, br, s, NH); *m/z* 423 (^{35}Cl, M^+), 403, 226, and 206 (base).

Reaction of the Dihydropyridine (**1**) *with Sodium Cyanide in Dimethylformamide.*—Sodium cyanide (0.1 g, 2.14 mmol) was added to a solution of the dihydropyridine (**1**) (1.0 g, 2.14 mmol) in dry dimethylformamide (15 ml) at 60 °C. The solution was stirred for 20 min, then cooled, diluted with ether (200 ml), and washed with saturated brine (4 × 100 ml). The ether was removed by distillation at atmospheric pressure leaving an oil which was triturated with ice-cold pentane. The pentane solution was decanted off and the residue recrystallised from propan-2-ol to give 3-*methyl* 5-(1-*methylethyl*) 2-(*fluoromethyl*)-6-*methylpyridine*-3,5-*dicarboxylate* (**4**) (0.45 g, 77%), m.p. 72—73 °C (Found: C, 58.2; H, 6.25; F, 6.8; N, 5.2. $C_{13}H_{16}FNO_4$ requires C, 58.0; H, 5.9; F, 7.1; N, 5.2%); $\nu_{max.}$ 1 720 (C=O), 1 710 (C=O), and 1 600 cm^{-1} (C=N); $\lambda_{max.}$ 270 (log ε 3.48) and 232 nm (4.03); δ_H 1.40 [6 H, d, *J* 6 Hz, $(CH_3)_2CH$], 2.91 (3 H, s, 6-CH_3), 3.96 (3 H, s, OCH_3), 5.29 [1 H, m, $CH(CH_3)_2$], 5.84 (2 H, d, J_{HF} 47 Hz, CH_2F), and 8.70 (1 H, s, pyridine 4-H); δ_C 21.9 [$(CH_3)_2CH$], 25.1 (6-CH_3), 52.6 (CH_3O), 69.6 (CHO), 82.6 (d, $^1J_{CF}$ 87.6 Hz, CH_2F), 121.9 (C-5), 125.6 (d, $^3J_{CF}$ 2.1 Hz, C-3), 140.9 (C-4), 158.1 (d, $^2J_{CF}$ 15.7 Hz, C-2), 162.9 (C-6), 165.1, and 165.3 (CO_2); *m/z* 269 (M^+), 238, 227, 210, 196, and 43 (base).

The pentane solution was concentrated at atmospheric pressure leaving an oil, which was purified by bulb-to-bulb distillation giving 1-chloro-4-fluoro-2-(trifluoromethyl)benzene (**3**) (0.3 g, 72%), b.p. 65 °C (bath temp.) at 25 mmHg (lit.,[4] 50—55 °C at 12 mmHg); δ_H 7.19 (1 H, dt, J_{HH} 9 and 2.5, J_{HF} 9 Hz, 5-H), 7.42 (1 H, dd, J_{HH} 2.5, J_{HF} 9 Hz, 3-H), and 7.47 (1 H, dd, J_{HH} 9, J_{HF} 5 Hz, 6-H); *m/z* 198 (^{35}Cl, M^+), 179 and 163 (base), identical by spectroscopy and chromatography with an authentic sample.

Reactions of the Dihydropyridines (**31a—e**) *with Sodium Cyanide in Dimethylformamide.*—The title compounds were treated with equimolar quantities of sodium cyanide by the foregoing procedure.

(i) The dihydropyridine (**31a**) (1 g) gave *methyl* (1-*methylethyl*) 2,6-*dimethylpyridine*-3,5-*dicarboxylate* (**35a**) (0.5 g, 89%), m.p. 89—90 °C (from cyclohexane) (Found: C, 62.3; H, 6.75; N, 5.45. $C_{13}H_{17}NO_4$ requires C, 62.1; H, 6.8; N, 5.6%); $\nu_{max.}$ 1 720 cm^{-1} (C=O); $\lambda_{max.}$ 280 (log ε 3.39), 271 (3.49), and 234 nm (3.99); δ_H 1.39 [6 H, d, *J* 6.5 Hz, $CH(CH_3)_2$], 2.64 (3 H, s, CH_3), 2.65 (3 H, s, CH_3), 3.93 (3 H, s, OCH_3), 5.26 [1 H, m, $CH(CH_3)_2$], 8.65 (1 H, s, pyridine 4-H); *m/z* 251 (M^+) and 209 (base).

(ii) The dihydropyridine (**31b**) (0.1 g) gave dimethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**35b**) (0.04 g, 76%), m.p. 99—100 °C (lit.,[18] 101—102 °C).

(iii) The dihydropyridine (**31c**) (0.1 g) gave diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**35c**) (0.035 g, 63%), m.p. 72—74 °C (lit.,[19] 73 °C).

(iv) The dihydropyridine (**31d**) (0.1 g) gave bis-(1-methylethyl) 2,6-dimethylpyridine-3,5-dicarboxylate (**35d**) (0.045 g, 77%), m.p. 63—65 °C (lit.,[20] 65—66 °C).

(v) The dihydropyridine (**31e**) (1.0 g) gave 2,6-dimethylpyridine-3,5-dicarbonitrile (**35e**) (0.2 g, 45%), m.p. 120 °C (lit.,[21] 118—120 °C).

Reactions of the Lactones (**6**) *and* (**36**) *with Sodium Cyanide in Dimethylformamide.*—The dihydropyridine lactone (**6**) (1.0 g, 2.3 mmol) and sodium cyanide (0.11 g, 2.2 mmol) in dry dimethylformamide (30 ml) were heated at 100 °C for 1 h. The cooled solution was poured into water and the suspension extracted with ether. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated at atmospheric pressure. The residue was washed with ice-cold light petroleum (b.p. 40—60 °C). The washings were concentrated at atmospheric pressure giving compound (**3**) as a pale yellow oil (0.15 g, 33%), identical (t.l.c., n.m.r., and mass spectrum) with authentic material. The solid was recrystallised from propan-2-ol to give (1-*methylethyl*) 2-*methyl*-5-*oxo*-7H-*furo*[3,4-b]*pyridine*-3-*carboxylate* (**37**) (0.31 g, 58%), m.p. 142—143 °C (Found: C, 61.05; H, 5.4; N, 5.8. $C_{12}H_{13}NO_4$ requires C, 61.3; H, 5.5; N, 5.95%); $\nu_{max.}$ 1 760 (lactone C=O), 1 705 (ester C=O), and

1 620 cm^{-1} (C=C); $\lambda_{max.}$ 274 (log ε 3.68) and 230 nm (3.90); δ_H 1.41 [6 H, d, $CH(CH_3)_2$], 2.97 (3 H, s, CH_3), 5.28 [1 H, m, $CH(CH_3)_2$], 5.34 (2 H, s, CH_2O), and 8.66 (1 H, s, pyridine 4-H); *m/z* 235 (M^+), and 193 (base).

By using the same method the dihydropyridine lactone (**36**) gave *methyl* 2-(*fluoromethyl*)-5-*oxo*-7H-*furo*[3,4-b]*pyridine*-3-*carboxylate* (**38**) (0.15 g, 28%), m.p. 107—109 °C (Found: C, 52.8; H, 3.4; F, 8.6; N, 6.3. $C_{10}H_8FNO_4$ requires C, 53.3; H, 3.55; F, 8.4; N, 6.2%); $\nu_{max.}$ 1 770 (lactone C=O) and 1 705 cm^{-1} (ester C=O); $\lambda_{max.}$ 263 nm (log ε 3.59); δ_H 4.0 (3 H, s, OCH_3), 5.45 (2 H, s, CH_2O), 6.0 (2 H, d, J_{HF} 46 Hz, CH_2F), and 8.82 (1 H, s, pyridine 4-H); *m/z* 225 (M^+) and 194 (base).

Reaction of the Dihydropyridine (**32**) *with Sodium Cyanide in Dimethylformamide.*—The dihydropyridine (**32**) (0.1 g, 0.18 mmol) and sodium cyanide (9 mg, 0.18 mmol) in dry DMF (5 ml) were heated at 60 °C for 45 min. Work-up in the usual way followed by recrystallisation of the residue from light petroleum gave *diethyl* 4-[3-*chloro*-6-*fluoro*-2-(*trifluoromethyl*)*phenyl*]-2,6-*bis*(*trifluoromethyl*)-1,2-*dihydropyridine*-3,5-*dicarboxylate* (**33**) (0.05 g, 50%), m.p. 127—129 °C (Found: C, 43.1; H, 2.4; Cl, 5.9; N, 2.7. $C_{20}H_{14}ClF_{10}NO_4$ requires C, 43.1; H, 2.5; Cl, 6.3; N, 2.5%); $\nu_{max.}$ 3 300 (N–H), 1 710 (C=O), and 1 695 cm^{-1} (C=O); δ_H 0.92 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.07 (3 H, t, *J* 7 Hz, CH_3CH_2), 4.40 (4 H, m, 2 × CH_3CH_2), 5.35 (1 H, d, J_{HH} 6 Hz, NH), 5.48 (1 H, dq, J_{HH} 6, J_{HF} 10 Hz, dihydropyridine 2-H), 7.16 (1 H, dd, J_{HH} 9, J_{HF} 11 Hz, aryl 5-H), and 7.50 (1 H, dd, J_{HH} 9, J_{HF} 5 Hz, aryl 4-H); *m/z* 557 (^{35}Cl, M^+), 528, 512, and 488 (base, $M^+ - CF_3$).

Diethyl 2,6-*Bis*(*trifluoromethyl*)*pyridine*-3,5-*dicarboxylate* (**34**).—A solution of the dihydropyridine (**32**) (0.1 g, 0.18 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.028 g, 0.18 mmol) in dry THF (20 ml) was heated at reflux under nitrogen for 20 min. The cooled solution was poured into brine and the product extracted into ether. Evaporation of the extract followed by drying the residue at 0.1 mmHg for 8 h afforded *compound* (**34**) (0.055 g, 85%) as a pale yellow oil which resisted attempts to induce crystallisation (Found: C, 43.5; H, 3.1; N, 3.9. $C_{13}H_{11}F_6NO_4$ requires C, 43.5; H, 3.1; N, 3.9%); $\nu_{max.}$ 1 710 cm^{-1} (C=O); δ_H 1.42 (6 H, t, *J* 7 Hz, CH_3CH_2), 4.50 (4 H, q, *J* 7 Hz, CH_3CH_2), and 8.50 (1 H, s, pyridine 4-H); *m/z* 360 (M^+ + H), 332, and 314 (base).

Reactions of the Dihydropyridines (**7**)—(**27**) *with Sodium Cyanide in Dimethylformamide: General Procedure.*—A solution of the dihydropyridine (0.2 mmol) in dry dimethylformamide (10 ml) was heated in an oil-bath maintained at the required temperature (±2 °C) by means of a Heidolph stirrer-hotplate and contact thermometer. Sodium cyanide (10 mg, 0.2 mmol) was added with stirring. Samples (*ca.* 0.2 ml) were withdrawn at intervals (every 2 min for the first 10 min, then every 5 min), and quenched by addition to saturated brine (1 ml) and ethyl acetate (0.5 ml), and the organic extract was monitored by t.l.c. on silica (5% ethyl acetate–dichloromethane as eluant). The reactions were followed until no starting material remained (by t.l.c.) or for 3 h, as appropriate. The remaining mixture was then cooled and poured into water, and the products were extracted into ether. The ether was removed by distillation at atmospheric pressure and the crude residue was analysed by n.m.r. and g.l.c.–mass spectrometry, with authentic starting materials and products for comparison. The results are summarised in Table 2.

Reactions of the Dihydropyridine (**1**) *with Other Bases and in Other Solvents.*—These experiments were carried out by the same general procedure but with equivalent amounts of the appropriate base and solvent. The results are shown in Table 1.

Reaction of the Dihydropyridine (**1**) *with Sodium Hydride and* N-(2-*Bromoethyl*)*phthalimide.*—The dihydropyridine (**1**) (5.0 g, 11 mmol) in dry DMF (60 ml) was added over 5 min to a stirred suspension of sodium hydride (0.56 g of 50% oil dispersion; 12 mmol) in dry DMF (100 ml) at 0 °C under nitrogen. The resulting mixture was stirred at 0 °C until gas evolution had ceased; a clear deep red solution was obtained. A solution of *N*-(2-bromoethyl)phthalimide (2.8 g, 11 mmol) in dry DMF (60 ml) was added over 3 min and the temperature was allowed to rise to 20 °C over 1 h. The solution was stirred for a further 2 h then poured onto crushed ice (500 g), and the products were extracted into ethyl acetate (3 × 300 ml). The combined extracts were washed with water (3 × 200 ml), dried ($MgSO_4$), and concentrated at atmospheric pressure to a yellow oil which was separated by column chromatography on silica [dichloromethane–ethyl acetate (4%) as eluant]. Five principal fractions were obtained, as follows [fractions (i)—(iii) were identified by spectroscopic and chromatographic comparison with authentic materials].

(i) 1-Chloro-4-fluoro-2-(trifluoromethyl)benzene (**3**) (1.0 g, 48%).

(ii) 2-Ethenyl-1*H*-isoindole-1,3(2*H*)-dione (1.0 g, 53%).

(iii) 3-Methyl 5-(1-methylethyl) 2-(fluoromethyl)-6-methylpyridine-3,5-dicarboxylate (**4**) (1.8 g, 61%).

(iv) A mixture of *R**,*R**- and *R**,*S**-isomers of 3-*methyl* 5-(1-*methylethyl*) 2-[*fluoro*-(2,3,5,9b-*tetrahydro*-5-*oxo*-*oxazolo*[2,3-a]*isoindol*-9b-*yl*)*methyl*]-6-*methylpyridine*-3,5-*dicarboxylate* (**40**) (0.88 g, 18%), m.p. 178—180 °C (from ethanol) (Found: C, 62.2; H, 5.1; F, 4.6; N, 6.35. $C_{23}H_{23}FN_2O_5$ requires C, 62.4; H, 5.2; F, 4.3; N, 6.3%); $\nu_{max.}$ 1 730 (C=O) and 1 700 cm^{-1} (C=O); $\lambda_{max.}$ 234 nm (log ε 3.89); δ_H 1.35 and 1.40 (2 × 6 H, d, *J* 6 Hz, CH_3CH), 2.48 and 2.89 (2 × 3 H, s, pyridine 6-CH_3), 3.20 and 3.31 (2 × 1 H, m, CHN), *ca.* 3.95 and 4.17 (2 × 1 H, m, CHN), 3.93 and 3.97 (2 × 3 H, s, CO_2CH_3), *ca.* 3.95 and 4.09 (2 × 1 H, m, CHO), 4.21 and 4.40 (2 × 1 H, m, CHO), 5.21 and 5.30 [2 × 1 H, septet, *J* 6 Hz, $(CH_3)_2CH$], 6.99 and 7.23 (2 × 1 H, d, J_{HF} 46 Hz, CHF), 7.45—7.65 (2 × 3 H, m, aryl 7-, 8-, and 9-H), 7.74 and 7.97 (2 × 1 H, d, aryl 6-H), and 8.61 and 8.69 (2 × 1 H, s, pyridine 4-H); *m/z* 411 (highest mass, $M^+ - OCH_3$) and 174 (base); fast atom bombardment: *m/z* 443 (M^+ + H). These isomers could not be adequately separated by chromatography. N.m.r. integration indicates an essentially equal mixture.

(v) 3-*Methyl* 5-(1-*methylethyl*) 2-(*fluoromethyl*)-6-[(2,3,5,9b-*tetrahydro*-5-*oxo*-*oxazolo*[2,3-a]*isoindol*-9b-*yl*)*methyl*]-*pyridine*-3,5-*dicarboxylate* (**41**) (0.19 g, 4%) as an amorphous glass which could not be induced to crystallise. Fully satisfactory elemental analyses could not be obtained, but spectroscopic data are fully in agreement with the proposed structure; δ_H 1.40 [6 H, 2 × d, $(CH_3)_2CH$, *J* 6 Hz], 3.10 (1 H, m, CHN), 3.85 (1 H, d, *J* 13 Hz, pyridine 6-CH), 3.95 (2 H, m, CH_2), 4.00 (3 H, s, CO_2CH_3), 4.15 (1 H, m, CHO), 4.60 (1 H, d, *J* 13 Hz, pyridine 6-CH), 5.25 [1 H, septet, $CH(CH_3)_2$], 5.5—5.7 (2 H, AB part of ABX, J_{HH} 15, J_{HF} 45 Hz, CH_2F), 7.42 (1 H, m, ArH), 7.57 (2 H, m, ArH), 7.70 (1 H, m, aryl 6-H), and 8.50 (1 H, s, pyridine 4-H); *m/z* 442 (M^+), 411, 383, and 174 (base).

The chemical shifts of the four aliphatic protons of the tetrahydro-oxazolo[2,3-*a*]isoindol-5-one nucleus of (**40**) and (**41**) are in excellent agreement with those reported by Aeberli and Houlihan[22] for simpler derivatives.

Reaction of the Dihydropyridine (**1**) *with Sodium Deuteroxide in* [$^2H_6$]*Dimethyl Sulphoxide* (*N.m.r. Study*).—Sodium deuteroxide solution (40% solution in ^2H_2O; 0.02 ml, 0.2 mmol) was added to a solution of the dihydropyridine (**1**) (30 mg, 0.064 mmol) in [$^2H_6$]dimethyl sulphoxide (0.5 ml). The resulting solution was placed in a tube in the spectrometer probe at 23 °C and n.m.r. spectra were run at 5 min intervals. After 45 min the spectrum showed signals corresponding to (**4**), with no

detectable deuterium incorporation, and to monodeuterio-(**3**), δ 7.60 (1 H, t, J_{HH} 9, J_{HF} 9 Hz, 5-H) and 7.77 (1 H, dd, J_{HH} 9, J_{HF} 5 Hz, 6-H) [in the same solvent (**3**) shows 7.60 (1 H, dt, J_{HH} 9 and 2.5 Hz, J_{HF} 9 Hz, 5-H) and 7.74—7.80 (2 H, m, 3-H and 6-H).

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References

1 A. Hantzsch, *Leibigs Ann. Chem.*, 1882, **215**, 1; U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1.
2 F. Bossert, H. Meyer, and E. Wehinger, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 762; J. Prous, P. Blancafort, J. Castañer, M. N. Serradell, and N. Mealy, *Drugs of the Future*, 1981, **6**, 427.
3 H. Meyer, S. Kazda, and P. Bellemann, *Annu. Rep. Med. Chem.*, 1983, **18**, 79; P. M. VanHoutte and R. A. Cohen, *Am. J. Cardiol.*, 1983, **52**, 99A; 'Calcium Channel Blocking Agents in the Treatment of Cardiovascular Disorders,' eds. P. H. Stone and E. M. Antman, Futura, Mount Kisco, New York, 1983.
4 A. J. G. Baxter, J. Dixon, K. Gould, T. McInally, and A. C. Tinker, Eur. Pat. Appl., 125 803/1984; R. G. Humphries and S. E. O'Connor, *J. Cardiovasc. Pharmacol.*, 1988, **11**, 332.
5 A. J. G. Baxter, J. Dixon, K. Gould, and A. C. Tinker, Eur. Pat. Appl., 174 131/1986.
6 T. McInally and A. C. Tinker, unpublished work.
7 A. J. G. Baxter, J. Dixon, and K. Gould, Eur. Pat. Appl., 169 009/1986.
8 A. I. Shatenshtein, *Adv. Phys. Org. Chem.*, 1963, **1**, 155.
9 D. K. Olsen, B. E. Torian, C. D. Morgan, and L. L. Braun, *J. Org. Chem.*, 1980, **45**, 4049.
10 S. Naturo, K. Shimakawa, H. Mizuta, H. Uno, and H. Nishimura, *Heterocycles*, 1981, **16**, 1089.
11 C. J. Wharton and R. Wrigglesworth, *J. Chem. Soc., Perkin Trans. 1*, 1985, 809.
12 O. Augosto, H. S. Beilan, and P. R. Ortiz de Montellano, *J. Biol. Chem.*, 1982, **257**, 11288; R. H. Bocker and F. P. Guengerich, *J. Med. Chem.*, 1986, **29**, 1596.
13 B. Loev and K. M. Snader, *J. Org. Chem.*, 1965, **30**, 1914.
14 R. G. R. Bacon and B. A. Osuntogun, *J. Chem. Soc., Chem. Commun.*, 1979, 1159.
15 D. D. Perrin, W. L. F. Armarego, and D. R. Perrin, 'Purification of Laboratory Chemicals,' Pergamon, Oxford, 1980.
16 A. J. G. Baxter, J. Dixon, T. McInally, and A. C. Tinker, Eur. Pat. Appl., 225 175/1987.
17 H. Meyer, E. Wehinger, F. Bossert, and D. Scherling, *Arzneim.-Forsch.*, 1983, **33**, 106.
18 J. L. Kurz, R. Hutton, and F. H. Westheimer, *J. Am. Chem. Soc.*, 1961, **83**, 584.
19 E. E. Ayling, *J. Chem. Soc.*, 1938, 1014.
20 Ya. R. Uldrikis, G. Ya. Dubur, I. V. Dipan, and B. S. Chekavichus, *Khim. Geterosikl. Soedin.*, 1975, 1230.
21 J. Kuthan, E. Janeckova, and M. Havel, *Collect. Czech. Chem. Commun.*, 1964, **29**, 143.
22 P. Aberli and W. J. Houlihan, *J. Org. Chem.*, 1969, **34**, 165.

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