The Synthesis of 3-(4-Aminotetrafluorophenyl)-3-ethylpiperidine-2,6-dione; a Fluorinated Derivative of Aminoglutethimide

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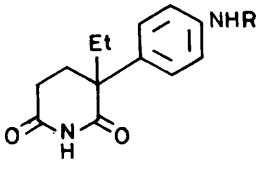
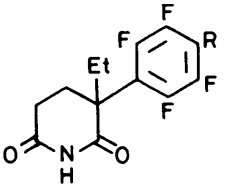
In investigating the role of the amino function of aminoglutethimide [3-(4-aminophenyl)-3-ethylpiperidine-2,6-dione, (**1**)] in the inhibition of the cholesterol side-chain cleavage enzyme system desmolase and the estrogen-forming system aromatase, 4-amino-2,3,5,6-tetrafluoroglutethimide (**4**) has been synthesised. Attempts to proceed *via* 2,3,5,6-tetrafluoro-4-nitroglutethimide (**5**) failed due to the marked susceptibility of the fluorine substituents *ortho* to the nitro group to nucleophilic displacement. Compound (**4**) was prepared *via* pentafluoro-glutethimide (**6**), and exhibited moderate inhibition of desmolase but was a very weak inhibitor of aromatase.

Aminoglutethimide (**1**) was first introduced into clinical use in 1958 as an anticonvulsant drug[1] but was subsequently withdrawn because of its adverse effects on adrenal steroidogenesis. It is now being used increasingly in the treatment of hormone-dependent metastatic breast carcinoma.[2,3] Inhibition of tumour growth is believed to be due to interference with estrogen biosynthesis, particularly by inhibition of the conversion of cholesterol into pregnenolone (mediated by desmolase) and of the androgens, androstene-3,17-dione and testosterone, into the estrogens, estrone and estradiol (mediated by aromatase). The major pathway of metabolism of aminoglutethimide in



(**1**) R = H
(**2**) R = Ac
(**3**) R = OH



(**4**) R = NH_2
(**5**) R = NO_2
(**6**) R = F

humans is *N*-acetylation (**2**), and the drug also induces its own metabolism to give the *N*-hydroxy derivative (**3**). The metabolic pathways are adverse in that the enzyme inhibitory activities of the metabolites are markedly inferior to those of the parent drug. If aminoglutethimide could be modified so that the foregoing metabolic pathways were retarded or blocked without compromising the enzyme inhibitory activity, then a potentially more effective drug could result. It should be possible to limit such metabolism by reducing the nucleophilicity of the amine nitrogen. This could be achieved by introducing four fluorine substituents into the aryl ring to give 4-amino-2,3,5,6-tetrafluoroglutethimide (**4**). It is known[4] that polyfluoroarylamines undergo *N*-acetylation with difficulty. Moreover if the reduced activity of compound (**2**) is due, at least in part, to steric inhibition of binding to the enzyme by the *N*-acetyl moiety, then this effect will be absent from the tetrafluoro analogue (**4**). Although an amino group appears to be essential for enzyme inhibitory activity in the aminoglutethimide series, the role of the amino group is not fully understood. For example, it could be involved in hydrogen bonding at a protein binding site or in chelating to the iron in the haem moiety of the enzyme. By analogy with aniline (pK_a 4.6[5]) and pentafluoroaniline (pK_a −0.36[6]) the basicity of the amino group in compound (**4**) will be much lower than in compound (**1**), thereby reducing hydrogen bonding and chelation by electron donation from the amine nitrogen but increasing the acidity of the amino hydrogens and hence their hydrogen bonding capability.

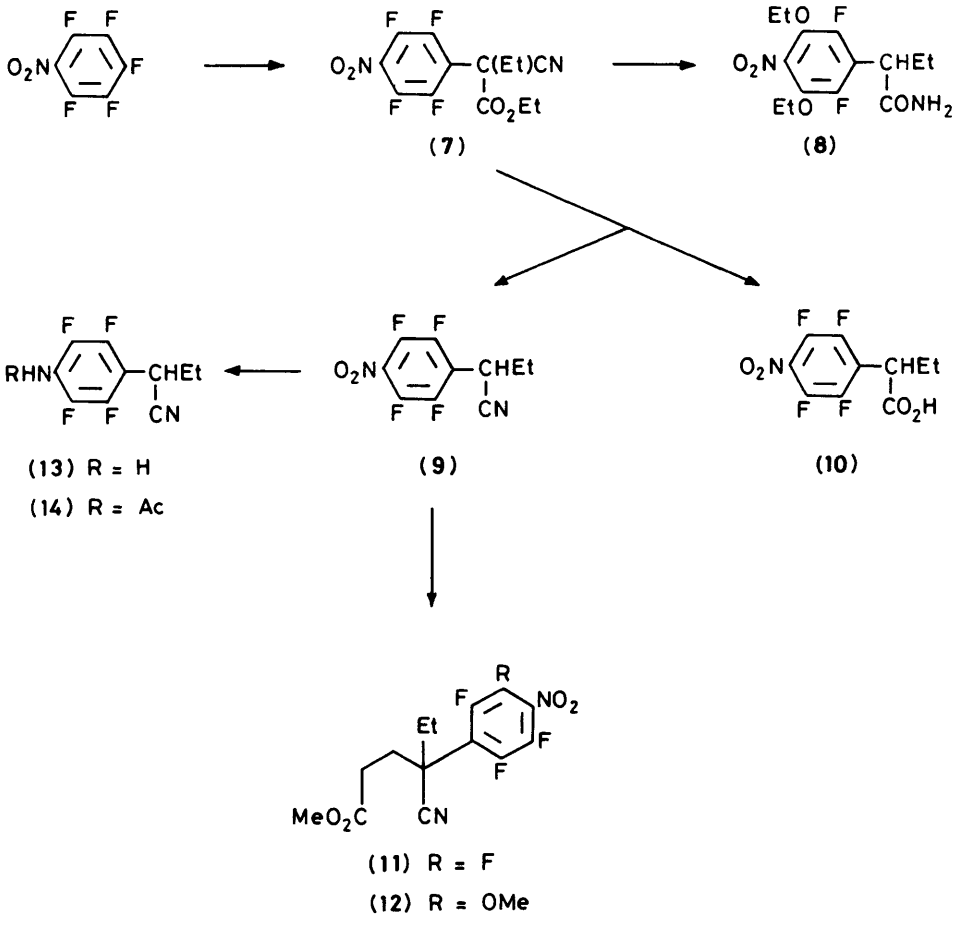
Two viable retrosynthetic pathways from compound (**4**) were envisaged, namely *via* the 2,3,5,6-tetrafluoro-4-nitrophenyl derivative (**5**) and reduction, or *via* the pentafluorophenyl derivative (**6**) and nucleophilic aromatic substitution of the *para*-fluorine with ammonia. A synthesis from pentafluoroaniline was precluded because of its known susceptibility to *meta* substitution with nucleophiles.[7]

The synthesis of the 2,3,5,6-tetrafluoro-4-nitrophenyl derivative (**5**) from commercially available pentafluoronitrobenzene required a nucleophilic substitution *para* to the nitro group with a suitable carbon nucleophile. The only literature precedents employing an aliphatic carbon nucleophile involve exclusive displacement of fluorine *ortho* to the nitro group[8] or displacement of the nitro group.[9] However, it seemed likely that the use of a solvent of higher polarity and an increased degree of dissociation of the metal cation and its counter-anion (*e.g.*, by the use of a potassium salt in DMF) should promote displacement of fluorine *para* to the nitro group.[10]

The strategy employed is illustrated in Scheme 1. Treatment of pentafluoronitrobenzene with the potassium salt of ethyl cyanoacetate in anhydrous DMF afforded an uncharacterisable brick-red solid. However, treatment with the potassium salt of ethyl 2-cyanobutyrate[11] in anhydrous DMF under mild conditions gave 65% of the desired 4-substituted product (**7**). This is the first reported example of a substitution at the 4-position of pentafluoronitrobenzene using an aliphatic carbon nucleophile.

Although selective nucleophilic displacement of the *para*-fluorine substituent in pentafluoronitrobenzene had been achieved, the susceptibility of the fluorine substituents *ortho* to the nitro group in the product to nucleophilic attack subsequently proved troublesome. Thus, attempts to hydrolyse/decarboxylate compound (**7**) using aqueous ethanolic potassium hydroxide afforded mainly 2-(3,5-diethoxy-2,6-difluoro-4-nitrophenyl)butyramide (**8**). This problem was circumvented by the use of an aqueous potassium hydroxide medium, with vibro-stirring of the heterogeneous mixture which gave a reasonable yield of the de-ethoxycarbonylated product (**9**). Improved yields were obtained by use of a glacial acetic acid–conc. sulphuric acid–water system, which afforded 68% of compound (**9**) along with 18% of the acid (**10**).

Introduction of the C-4,5,6 portion of the glutarimide ring into compound (**9**) was approached *via* a Michael condensation with methyl propenoate. Using Triton B as the basic catalyst,



Scheme 1.

reaction at 65 °C for 8 h afforded a 3:1 mixture of the Michael adducts (**11**) and (**12**), the latter being formed by nucleophilic attack of methoxide derived from the catalyst. This latter reaction could be suppressed, but not prevented, by using shorter reaction times. Clean preparative separation of compounds (**11**) and (**12**) was impossible, and so other reaction conditions were investigated. When t-butyl alcohol or acetonitrile was used as solvent, poor-yielding and non-reproducible reactions resulted and, perhaps surprisingly,[12] no reaction occurred in the absence of solvent. Several other reagents, including potassium fluoride–18-crown-6, sodium hydride and pyridine, also proved unsatisfactory.

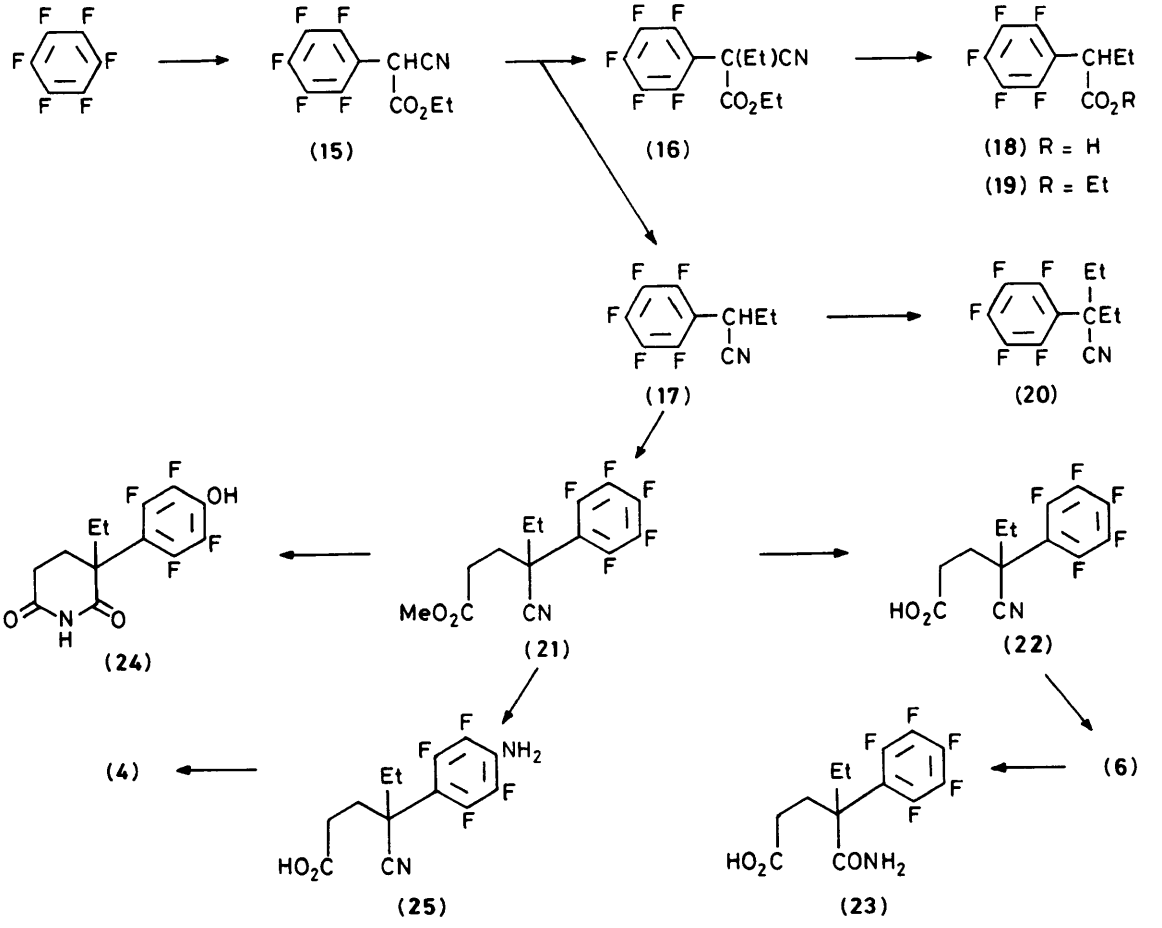
In seeking to avoid the aforementioned problems associated with the nitro group in compound (**9**), reduction to the corresponding amine (**13**) was now attempted. However, catalytic hydrogenation of compound (**9**)[5] at −5 °C gave a complex mixture of products due to concomitant reduction of the nitrile group and hydrogenolysis of C–F bonds in the aryl ring. This difficulty was overcome by hydrogenating compound (**9**) in anhydrous, saturated ethanolic hydrogen chloride. The nitro group was the most readily hydrogenated function and the resulting amine (**13**) was precipitated as its hydrochloride.[4] In this manner a reasonable yield of the desired amine (**13**) was obtained. However, the *N*-acetate (**14**)[6] of compound (**13**), obtained under forcing conditions, using the method of Brooke,[4] failed to undergo a Michael condensation with methyl propenoate.

An alternative approach to compound (**4**), *via* amination of the pentafluorophenyl derivative (**6**), was therefore investigated, as illustrated in Scheme 2.

Treatment[13] of hexafluorobenzene with the potassium salt of ethyl cyanoacetate afforded the cyano ester (**15**) in good yield. Ethylation of the sodium hydride-generated anion of compound (**15**) with iodoethane afforded 75% of the expected monoethylated product (**16**), together with 11% of the de-ethoxycarbonylated nitrile (**17**). Extended reaction times could not drive the de-ethoxycarbonylation process to completion and extensive decomposition also occurred. The use of elevated reaction temperatures afforded significant amounts of the diethylated product (**20**) as indicated by n.m.r. spectroscopy. Initial attempts to hydrolyse compound (**16**) with acid gave the carboxylic acid (**18**) and small quantities of the ethyl ester (**19**), but conditions were found which gave the nitrile as the major component in a mixture of compounds (**17**) and (**18**).[12] Refluxing a solution of compound (**16**) in aqueous DMSO for extended periods or, for shorter times, in an aqueous DMSO solution containing sodium chloride,[14] also produced good yields of compound (**17**).

The C-4,5,6 portion of the glutarimide ring was then introduced into (**17**) by a Michael condensation with methyl propenoate in the presence of Triton B at 100 °C, to afford a good yield of the desired adduct (**21**).

An approach to the formation of the glutarimide ring by classical[1] cyclisation of a cyano acid was frustrated. Basic hydrolysis of compound (**21**) gave a complex mixture of products containing the 4-hydroxy compound (**24**), formed by nucleophilic displacement of the *para*-fluorine. However, compound (**22**) could be isolated after a short reaction time and cyclised under anhydrous acidic conditions to give compound (**6**) in moderate yield. A more facile procedure involved acid-



Scheme 2.

Table. Inhibition studies[15]

	I_{50} Values	
	Desmolase *	Aromatase †
Aminoglutethimide (**1**)	30 μM	8 μM
4-Amino-2,3,5,6-tetrafluoro-glutethimide (**4**)	200 μM	130 μM
Pentafluoroglutethimide (**6**)	Inactive	200 μM

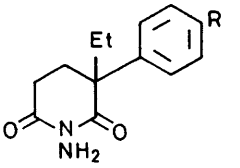
* Substrate concentration for desmolase = 14 μM (K_m = 4.5 μM cholesterol).
† Substrate concentration for aromatase = 1.5 μM (K_m = 0.13 μM testosterone).

catalysed cyclisation of compound (**21**) to afford compound (**6**) in almost quantitative yield.

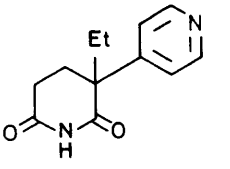
All that remained now was to introduce the *para*-amino group of the target compound (**4**). Treatment of compound (**6**) with an excess of aqueous ethanolic ammonia at 120 °C for 24 h gave a mixture of 4-amino-2,3,5,6-tetrafluorophenyl- and pentafluorophenyl-containing products, with the major component having structure (**23**). The low degree of regioselectivity between attack of ammonia on the pentafluorophenyl- and glutarimide rings suggested that a direct amination of the cyano ester (**21**) might be more profitable. Thus, reaction of compound (**21**) with aqueous ethanolic ammonia at 100 °C for 67 h afforded a mixture of four major components including (**25**), all of which contained the 4-amino-2,3,5,6-tetrafluorophenyl ring (^{19}F n.m.r. data). Cyclisation of this mixture under anhydrous acidic conditions afforded, albeit in low yield, 4-amino-2,3,5,6-tetrafluoroglutethimide (**4**), together with several unidentified components.

Enzyme Inhibition Studies.—The Table gives the inhibitory activity of aminoglutethimide (**1**), pentafluoroglutethimide (**6**), and 4-amino-2,3,5,6-tetrafluoroglutethimide (**4**) against desmolase and aromatase. As expected, compound (**6**), which has no basic group, was a very weak inhibitor of both desmolase and aromatase. Although compound (**4**) was a very weak inhibitor of aromatase, it showed most activity against desmolase.

These findings suggest that the essential role of the amino group in compound (**1**) is associated with the lone pair of electrons. The location of the basic function is of critical importance. Thus, whereas aminoglutethimide inhibits both aromatase and desmolase, *N*-aminoglutethimide (**26**) and *N*-



(**26**) R = H
(**27**) R = F



(**28**)

amino-4-fluoroglutethimide (**27**) are specific desmolase inhibitors, and 4-pyridylglutethimide (**28**)[12] is a specific aromatase inhibitor.

Experimental

M.p.s were determined using an Electrothermal or Gallenkamp apparatus and are uncorrected. I.r. spectra (liquids as films and solids as nujol mulls between sodium chloride discs) were obtained with a Perkin-Elmer 257 or Unicam SP 1050 spectrometer. N.m.r. spectra were recorded on a Perkin-Elmer R12B spectrometer; ^{1}H n.m.r. spectra at 60 MHz using tetramethylsilane as an internal standard, and ^{19}F n.m.r. spectra at 56.4 MHz using chlorotrifluoromethane as an internal standard. Mass spectra were determined with a Kratos M.S. 80 spectrometer, using the direct insertion method and an ionizing voltage of 70 eV. Polygram S1L N-HR/UV$_{254}$ silica gel plates were used for t.l.c., with visualisation of spots by u.v. light or iodine vapour. Silica gel (Merck, Kieselgel 60, 70–230 mesh ASTM type 7734) was used for all column chromatographic separations. G.l.c. analyses were carried out using a 3% dimethylsilicone gum (OV1) or Gas Chrom Q (80–120 mesh packing) and utilising flame ionisation detection.

Unless otherwise stated, organic extracts were combined, dried ($MgSO_4$), and concentrated on a rotary evaporator. Solvents were dried by standard procedures. All non-aqueous reactions were protected against atmospheric moisture by the use of silica gel or calcium chloride guard tubes.

Preparation of Ethyl 2-Cyano-2-(2,3,5,6-tetrafluoro-4-nitrophenyl)butyrate (**7**).—Ethyl 2-cyanobutyrate (14.6 g, 104 mmol) was added dropwise over 10 min to a rapidly stirred suspension of oven-dried potassium carbonate (14.5 g, 105 mmol) in dry dimethylformamide (DMF) (70 cm^3) at 150 °C. The resulting orange suspension was stirred whilst cooling slowly to room temperature over 1.5 h. Then, at 15—20 °C and with stirring, pentafluoronitrobenzene (20.0 g, 94 mmol) was added dropwise over 10 min, and the dark red solution was stirred for a further 15 min before being poured into ice–water (250 cm^3). Acidification with 20% v/v sulphuric acid separated a red oil from a yellow aqueous layer, and, after refrigeration for 1 h, the two layers were separated. The aqueous layer was extracted with diethyl ether (3 × 100 cm^3), the ethereal extracts combined with the organic layer, and the whole washed with water (100 cm^3), 10% aqueous sodium hydrogen carbonate (3 × 100 cm^3), and water (3 × 100 cm^3), dried ($MgSO_4$), and concentrated to a red oil (29.05 g). Traces of solvent and any unchanged starting materials were removed by distillation under reduced pressure, and the residue (24.91 g) was purified initially by adsorption chromatography (100 g column eluted with dichloromethane) to give an orange oil (23.72 g). Distillation under reduced pressure afforded the *title compound* (**7**) as a yellow liquid (20.53 g, 65%), b.p. 138—148 °C/0.1 mmHg (Found: C, 47.0; H, 3.1; F, 22.5; N, 8.2. $C_{13}H_{10}F_4N_2O_4$ requires C, 46.7; H, 3.0; F, 22.8; N, 8.4%); $\nu_{max.}$ 1 760 (C=O) and 2 250 cm^{-1} (C≡N); δ_H 1.17 (3 H, t, *J* 7 Hz, Me), 1.36 (3 H, t, *J* 7 Hz, Me), 2.47 (2 H, q, CH_2) and 4.40 (2 H, q, *J* 7 Hz, CO_2CH_2); δ_F 134.2 and 145.4 (4 F, AA′XX′ system, 3,5-F and 2,6-F).

The sodium hydrogen carbonate washings were acidified with 4M hydrochloric acid and extracted with diethyl ether (3 × 50 cm^3). The combined ethereal extracts washed with water (3 × 50 cm^3), dried ($MgSO_4$) and concentrated to a mobile orange liquid (1.0 g) which was not further investigated.

Reaction of Ethyl 2-Cyano-2-(2,3,5,6-tetrafluoro-4-nitrophenyl)butyrate (**7**) *with Aqueous Ethanolic Potassium Hydroxide*.—Ethyl 2-cyano-2-(2,3,5,6-tetrafluoro-4-nitrophenyl)butyrate (**7**) (0.70 g, 2.10 mmol) was added to a solution of potassium hydroxide pellets (0.47 g, 8.39 mmol) in absolute ethanol (5.3 cm^3) and water (2.3 cm^3), to give immediate formation of a deep purple one-phase system. Stirring was continued at room temperature for 115 h, when the deep red/brown solution above a white solid was acidified with 4M hydrochloric acid, concentrated under reduced pressure and then partitioned between water (25 cm^3) and diethyl ether (25 cm^3). The aqueous layer was separated and extracted with diethyl ether (3 × 25 cm^3), the combined ethereal solutions washed with 10% aqueous sodium hydrogen carbonate (3 × 25 cm^3) and water (25 cm^3), dried ($MgSO_4$), and concentrated to give a red oil (0.55 g); this was shown by ^{19}F n.m.r. spectroscopy to consist of a 2:1 mixture of two fluorine-containing compounds. The addition of a little diethyl ether followed by slow evaporation caused crystallisation to a pale brown solid, which was washed with hexane (5 cm^3) and then recrystallised from light petroleum (b.p. 60—80 °C) to afford 2-(3,5-diethoxy-2,6-difluoro-4-nitrophenyl)butyramide (**8**) as white needles, m.p. 97—98 °C; δ_H 0.90 (3 H, t, *J* 7 Hz, Me), 1.34 (6 H, t, *J* 7 Hz, Me), 2.10 (2 H, m, CH_2), 3.81 (1 H, dd, *J* 10 and 6 Hz, CH), 4.22 (2 H, q, *J* 7 Hz, OCH_2), and 5.98 (2 H, s, NH_2 disappeared in D_2O); δ_F 133 (2 F, s, 2,6-F), identified as the major component of the crude product. The compound decomposed with time and the reaction was not further investigated.

Preparation of 2-(2,3,5,6-Tetrafluoro-4-nitrophenyl)butyronitrile (**9**).—A stirred mixture of compound (**7**) (25.0 g, 74.9 mmol), glacial ethanoic acid (150 g), concentrated sulphuric acid (12 g) and water (150 g) was refluxed at 150 °C for 94 h. The cooled clear yellow solution was poured into ice–water (1 000 cm^3) and extracted with diethyl ether (3 × 250 cm^3) and the combined ethereal extracts were washed with water (2 × 250 cm^3). The ethereal extracts were then washed, with vigorous stirring over 3 h, with saturated aqueous sodium hydrogen carbonate (500 cm^3) and then shaken with more 10% aqueous sodium hydrogen carbonate (2 × 250 cm^3). Only when no further effervescence was observed and the sodium hydrogen carbonate layer was weakly coloured was the ethereal layer washed with water (2 × 250 cm^3), dried ($MgSO_4$) and concentrated to afford an orange oil (15.0 g). Distillation under reduced pressure in a 10 cm Vigreux column afforded the *title compound* (**9**) as a pale green liquid, b.p. 125—129 °C/0.1 mmHg (13.3 g, 68%) (Found: C, 45.5; H, 2.3; F, 29.4; N, 10.4. $C_{10}H_6F_4N_2O_2$ requires C, 45.8; H, 2.3; F, 29.0; N, 10.7%); $\nu_{max.}$ 2 250 cm^{-1} (C≡N); δ_H 1.60 (3 H, t, *J* 7 Hz, Me), 2.11 (2 H, m, CH_2), and 4.17 (1 H, t, *J* 7 Hz, CH); δ_F 138.1 and 145.9 (4 F, AA′XX′ system, 3,5-F and 2,6-F).

The red sodium hydrogen carbonate washings were acidified with 4M hydrochloric acid and the resulting pale yellow solution was extracted with diethyl ether (3 × 250 cm^3); the combined ethereal extracts were then washed with water (2 × 250 cm^3), dried ($MgSO_4$), and concentrated to afford a red oil (4.73 g). Distillation under reduced pressure afforded 2-(2,3,5,6-*tetrafluoro-4-nitrophenyl)butyric acid* (**10**) as a pale yellow liquid, b.p. 154—159 °C 0.15 mmHg, which crystallised on scratching to give a pale yellow solid, m.p. 72—76 °C. Recrystallisation from water gave pale yellow crystals, m.p. 76—78 °C (3.75 g, 18%) (Found: C, 43.0; H, 2.6; F, 26.8; N, 5.3. $C_{10}H_7F_4NO_4$ requires C, 42.7; H, 2.5; F, 27.0; N, 5.0%); $\nu_{max.}$ 1 710 (C=O) and 2 300—3 400 cm^{-1} (OH); δ_H 0.97 (3 H, t, *J* 7 Hz, Me), 2.15 (2 H, m, CH_2), 4.10 (1 H, dd, *J* 9 and 6 Hz, CH) and 11.66 (1 H, s, CO_2H disappeared in D_2O); δ_F 138.2 and 147.1 (4 F, AA′XX′ system, 3,5-F and 2,6-F).

Attempted Preparation of Methyl 4-Cyano-4-(2,3,5,6-tetrafluoro-4-nitrophenyl)hexanoate (**11**).—To a stirred mixture of 2-(2,3,5,6-tetrafluoro-4-nitrophenyl)butyronitrile (**9**) (4.75 g, 18.1 mmol) and methyl propenoate (4.75 g, 52.6 mmol), cooled in an

ice–water bath to 0—2 °C, was added dropwise Triton B (3 × 0.1 cm^3), at 1 min intervals. The dark purple solution was heated at 65 °C for 8 h after which it was cooled and acidified with 4M hydrochloric acid. The resulting orange solution was extracted with trichloromethane (2 × 50 cm^3) and the combined trichloromethane extracts were washed with water (3 × 30 cm^3), dried ($CaCl_2$), and concentrated to a red oil (5.88 g). Adsorption chromatography [200 g column eluted with dichloromethane–methylbenzene (80:20)] gave: (*i*) R_F 0.60, a green oil, identified as unchanged 2-(2,3,5,6-tetrafluoro-4-nitrophenyl)butyronitrile (**9**) (0.43 g, 9% recovery), (*ii*) R_F 0.47, a green oil, unidentified (0.44 g), and (*iii*) R_F 0.28, a green oil, identified as an inseparable mixture of the *title compound* (**11**) (2.27 g, 36%); δ_H 1.13 (3 H, t, *J* 7 Hz, Me), 2.28 (2 H, m, CH_2), 2.52 (4 H, A_2B_2, CH_2CH_2) and 3.66 (3 H, s, CO_2Me); δ_F 134.0 and 145.3 (4 F, AA′XX′ system, 3,5-F and 2,6-F); and methyl 4-cyano-4-(2,5,6-trifluoro-3-methoxy-4-nitrophenyl)hexanoate (**12**) (0.76 g, 12%). δ_H 1.15 (3 H, t, *J* 7 Hz, Me), 2.30 (2 H, m, CH_2), 2.53 (4 H, A_2B_2, CH_2CH_2), 3.64 (3 H, s, CO_2Me) and 4.07 (3 H, m, OMe); δ_F 127.0 (1 F, d, *J* 11 Hz, 2-F), 136.0 (1 F, d, *J* 21 Hz, 6-F), and 148.2 (1 F, dd, *J* 21 and 11 Hz, 5-F).

Preparation of 2-(4-*Amino*-2,3,5,6-*tetrafluorophenyl*)*butyronitrile* (**13**).—A solution of compound (**9**) (3.0 g, 11.5 mmol) in dry ethanol saturated with dry hydrogen chloride (120 cm^3) was hydrogenated over 10% palladinized charcoal (1.2 g) at 1 atm. Initially, hydrogenation was carried out at −8 °C in a salt–ice–water bath, and was continued over 6 h as the temperature rose slowly to room temperature. Hydrogenation was then continued at room temperature for 18 h before the mixture was neutralised to pH 7 with 4M sodium hydroxide. The catalyst was filtered off, washed with dichloromethane (100 cm^3), and the filtrate concentrated to provide an off-white solid which was partitioned between dichloromethane (150 cm^3) and water (150 cm^3). The aqueous layer was separated and extracted with dichloromethane (2 × 150 cm^3), and the combined dichloromethane extracts were washed with water (150 cm^3), dried ($MgSO_4$), and concentrated to provide a brown oil (1.80 g). Adsorption chromatography [200 g column, eluted with tetrachloromethane–trichloromethane (67:33)] gave: (*i*) R_F 0.46, a pale yellow solid, identified as 2-(4-*amino*-2,3,5,6-*tetrafluorophenyl*)*butyronitrile* (**13**), and recrystallised from dichloromethane–hexane to give a white solid, m.p. 76.5—78.0 °C (0.91 g, 34%) (Found: C, 51.8; H, 3.6; F, 32.9; N, 11.9. $C_{10}H_8F_4N_2$ requires C, 51.7; H, 3.5; F, 32.8; N, 12.1%); $\nu_{max.}$ 2 255 (C≡N) and 3 230, 3 370, and 3 470 cm^{-1} (NH); δ_H 1.08 (3 H, t, *J* 7 Hz, Me), 2.02 (2 H, m, CH_2), 3.94 (1 H, t, *J* 8 Hz, CH) and 4.18 (2 H, s, NH_2 disappeared in D_2O); δ_F 145.6 and 161.3 (4 F, AA′XX′ system, 2,6-F and 3,5-F) (*ii*) a mixture (0.73 g) containing compound (**13**) and at least three other components which were not investigated.

Preparation of 2-(4-*Acetamido*-2,3,5,6-*tetrafluorophenyl*)*butyronitrile* (**14**).—A stirred mixture of 2-(4-amino-2,3,5,6-tetrafluorophenyl)butyronitrile (**13**) (0.63 g, 2.72 mmol), acetic anhydride (0.59 g, 5.78 mmol) and concentrated sulphuric acid (2 drops) was refluxed on an oil-bath pre-heated to 150 °C for 5 min. To the cooled solution was added water (3 cm^3) and the temperature raised to 50 °C to hydrolyse the last traces of acetic anhydride. The cooled yellow residue was extracted with dichloromethane (3 × 2 cm^3) and the combined dichloromethane extracts were washed with water (2 × 2 cm^3), dried ($CaCl_2$), and concentrated to provide an orange oil (0.72 g). Adsorption chromatography on a 0.60 g portion [80 g column eluted with trichloromethane–methanol (99:1)] gave: (*i*) R_F 0.69, white crystals of unchanged compound (**13**) (0.04 g, 8% recovery), (*ii*) R_F 0.28, unidentified (0.08 g), and (*iii*) R_F 0.21, a yellow oil, identified as the *title compound* (**14**), which crystallised on, scratching to give a yellow solid (0.41 g, 66%). Recrystallisation of this from dichloromethane gave white crystals, m.p. 94—95 °C. (Found: C, 52.5; H, 3.6; F, 27.2; N, 9.9. $C_{12}H_{10}F_4N_2O$ requires C, 52.6; H, 3.6; F, 27.7; N, 10.2%); $\nu_{max.}$ 1 700 (C=O), 2 250 cm^{-1} (C≡N), and 3 280 cm^{-1} (NH); δ_H 1.11 (3 H, t, *J* 7 Hz, Me), 2.07 (2 H, m, CH_2), 2.20 (3 H, s, MeCO), 4.09 (1 H, t, *J* 8 Hz, CH), and 8.54 (1 H, s, NH disappeared in D_2O); δ_F 143.9 (4 F, AA′BB′ system).

Preparation of Ethyl 2-*Cyano*-2-*pentafluorophenylacetate* (**15**).—A rapidly stirred suspension of oven-dried potassium carbonate (70 g, 0.51 mol) in dry DMF (325 cm^3) was heated to 152 °C and ethyl cyanoacetate (56.5 g, 0.50 mol) was added dropwise over 15 min without further heating. The temperature was allowed to fall to 115 °C and was maintained there while hexafluorobenzene (93 g, 0.50 mol) was added dropwise over 2 h. The red mixture was then stirred at 115 °C for a further 3.5 h, cooled, and acidified with 20% v/v sulphuric acid. After refrigeration at 2 °C overnight, the yellow aqueous layer was decanted from the red organic layer and extracted with diethyl ether (4 × 250 cm^3). The combined organic layers were washed with water (2 × 250 cm^3), dried ($MgSO_4$), and concentrated to give a red oil (102.8 g). Distillation under reduced pressure in a 15 cm Vigreux column afforded the *title compound* (**15**) as a colourless liquid, b.p. 110—120 °C/0.45 mmHg, which crystallised on refrigeration at −20 °C to give a white solid, m.p. 34—36 °C (lit.,[13] 38—38.5° C) (95.6 g, 69%); $\nu_{max.}$ 1 770 (C=O) and 2 260 cm^{-1} (C≡N); δ_H 1.34 (3 H, t, *J* 7 Hz, Me), 4.35 (2 H, q, *J* 7 Hz, CH_2), and 5.11 (1 H, s, CH); δ_F 140.8 (2 F, m, 2,6-F), 151.3 (1 F, t, *J* 20 Hz, 4-F), and 160.7 (2 F, m, 3,5-F).

Reaction of Ethyl 2-*Cyano*-2-*pentafluorophenylacetate* (**15**) *with Iodoethane*.—Compound (**15**) (95.6 g, 0.34 mol) in dry DMF (340 cm^3) was added dropwise to a rapidly stirred suspension of sodium hydride pellets (10.05 g, 0.42 mol) in dry DMF (340 cm^3) over 1 h and the green solution heated at 85 °C for 17 h. To the cooled deep red solution was added, dropwise, iodoethane (270 g, 1.73 mol) over 1 h, and the mixture was heated at 75 °C for 24 h. The cooled dark red suspension was acidified with 5% v/v hydrochloric acid, and the yellow aqueous layer separated from the red organic layer, saturated with sodium chloride, and extracted with diethyl ether (3 × 250 cm^3). The combined organic layers were washed with 10% aqueous sodium metabisulphite (3 × 150 cm^3) and water (2 × 250 cm^3), dried ($MgSO_4$), and concentrated to give a brown oil (117.1 g). Careful distillation under reduced pressure in a 15 cm Vigreux column afforded *ethyl* 2-*cyano*-2-*pentafluorophenylbutyrate* (**16**) as a colourless liquid, b.p. 108—109/0.6 mmHg. Several early fractions contained significant amounts of 2-pentafluorophenylbutyronitrile (**17**) which could not be separated by distillation. The overall yield of ethyl 2-cyano-2-pentafluorophenylbutyrate (**16**) was 79.0 g (75%), and that of 2-pentafluorophenylbutyronitrile (**17**) was 9.2 g (11%). Adsorption chromatography [60 g column eluted with tetrachloromethane–dichloromethane (1:1)] on a mixture of (**16**) and (**17**) (0.33 g) gave: (*i*) R_F 0.46, compound (**16**) (0.25 g) (Found: C, 50.9; H, 3.2; F, 30.4; N, 4.7. $C_{13}H_{10}F_5NO_2$ requires C, 50.8; H, 3.3; F, 30.9; N, 4.6%); $\nu_{max.}$ 1 760 (C=O) and 2 240 cm^{-1} (C≡N); δ_H 1.15 (3 H, t, *J* 7 Hz, Me), 1.34 (3 H, t, *J* 7 Hz, Me), 2.45 (2 H, q, *J* 7 Hz, CH_2), and 4.36 (2 H, q, *J* 7 Hz, CO_2CH_2); δ_F 138.3 (2 F, m, 2,6-F), 152.8 (1 F, tt, *J* 20 and 3 Hz, 4-F), and 161.2 (2 F, m, 3,5-F); and (*ii*) R_F 0.34, 2-pentafluorophenylbutyronitrile (**17**) (0.06 g) (see later).

Preparation of 2-*Pentafluorophenylbutyric Acid* (**18**).—A mixture of compound (**16**) (20.0 g, 65.1 mmol), concentrated sulphuric acid (71 cm^3), and water (83 cm^3) was refluxed at 160 °C for 31 h. The cooled, red two-phase system was poured

onto ice (500 cm^3) and extracted with diethyl ether (3 × 200 cm^3); the combined ethereal extracts were washed with water (3 × 200 cm^3), dried ($MgSO_4$), and concentrated to give a red oil (18.9 g). Distillation under reduced pressure afforded (*i*) *ethyl 2-pentafluorophenylbutyrate* (**19**) as a very pale green liquid, b.p. 63—65 °C/0.5 mmHg (2.75 g, 15%) (Found: C, 51.4; H, 3.6; F, 33.6. $C_{12}H_{11}F_5O_2$ requires C, 51.5; H, 3.9; F, 33.7%); $\nu_{max.}$ 1 750 cm^{-1} (C=O); δ_H 0.92 (3 H, t, *J* 8 Hz, Me), 1.25 (3 H, t, *J* 7 Hz, Me), 2.10 (2 H, m, CH_2), 3.89 (1 H, dd, *J* 10 and 6 Hz, CH), and 4.20 (2 H, q, *J* 7 Hz, OCH_2); δ_F 142.1 (2 F, m, 2,6-F), 156.2 (1 F, t, *J* 21 Hz, 4-F), and 162.5 (2 F, m, 3,5-F) and (*ii*) the *title compound* (**18**) as a colourless liquid, b.p. 93—98 °C/0.6 mmHg, which crystallised with time to give a white solid, m.p. 56—58 °C (12.07 g, 73%) (Found: C, 46.9; H, 2.7; F, 37.8. $C_{10}H_7F_5O_2$ requires C, 47.2; H, 2.8; F, 37.4%); $\nu_{max.}$ 1 720 (C=O) and 2 380—3 420 cm^{-1} (acid OH); δ_H 0.92 (3 H, t, *J* 7 Hz, Me), 2.10 (2 H, m, CH_2), 3.96 (1 H, dd, *J* 10 and 6 Hz, CH), and 12.09 (1 H, s, CO_2H, disappeared in D_2O); δ_F 142.4 (2 F, m, 2,6-F), 156.1 (1 F, t, *J* 20 Hz, 4-F), and 162.9 (2 F, m, 3-5-F).

Preparation of 2-Pentafluorophenylbutyronitrile (**17**).—(*a*) A stirred mixture of ethyl 2-cyano-2-pentafluorophenylbutyrate (**16**) (30.0 g, 97.9 mmol), glacial acetic acid (210 g), concentrated sulphuric acid (15 g), and water (210 g) was refluxed at 140 °C for 130 h. The cooled two-phase colourless system was poured into ice–water (500 cm^3) and extracted with diethyl ether (3 × 250 cm^3); the combined ethereal extracts were washed with 10% aqueous sodium hydrogen carbonate (750 cm^3) with rapid stirring over 1 h and then water (100 cm^3), dried ($MgSO_4$), and concentrated to provide a pale yellow oil (15.6 g). Distillation under reduced pressure afforded the *title compound* (**17**) as a colourless liquid, b.p. 60—66 °C/0.15 mmHg (13.6 g, 59%) (Found: C, 51.3; H, 2.8; F, 39.9; N, 6.0. $C_{10}H_6F_5N$ requires C, 51.1; H, 2.5; F, 40.4; N, 6.0%); $\nu_{max.}$ 2 250 cm^{-1} (C≡N); δ_H 1.13 (3 H, t, *J* 7 Hz, Me), 2.02 (2 H, m, CH_2), and 4.06 (1 H, t, *J* 8 Hz, CH); δ_F 142.1 (2 F, m, 2,6-F), 153.8 (1 F, tt, *J* 20 and 2 Hz, 4-F), and 161.3 (2 F, m, 3,5-F).

The basic aqueous washings were acidified with 4M hydrochloric acid and extracted with diethyl ether (3 × 100 cm^3); the combined ethereal extracts were washed with water (100 cm^3), dried ($MgSO_4$), and concentrated to give a pale green oil which crystallised with time to provide a cream solid, identified as the title compound (**18**) (5.2 g, 21%).

(*b*) A stirred suspension of compound (**16**) (1.50 g, 4.89 mmol) and sodium iodide (1.72 g, 11.5 mmol) in dry DMF (3.5 cm^3) was heated to 150 °C. At 100 °C the system was homogeneous, and, on attaining 150 °C, carbon dioxide evolution was observed as the solution became dark red and opaque. After 4 h at 150 °C, the cooled brown suspension was poured onto ice (20 cm^3), acidified with 2M hydrochloric acid and extracted with ether (3 × 10 cm^3). The combined ethereal extracts were washed with water (3 × 20 cm^3), dried ($MgSO_4$) and concentrated to a yellow oil (0.50 g), identified by g.l.c. and n.m.r. as a 3:1 mixture of the *title compound* (**17**) and *3-cyano-3-pentafluorophenylpentane* (**20**); δ_H 1.08 (6 H, t, *J* 7 Hz, Me) and 2.13 (4 H, m, CH_2); δ_F 138.2 (2 F, m, 2,6-F), 154.6 (1 F, tt, *J* 21 and 3 Hz, 4-F) and 161.5 (2 F, m, 3,5-F).

(*c*) A stirred mixture of compound (**16**) (10.0 g, 32.6 mmol), dimethyl sulphoxide (25 cm^3), and water (10 cm^3) was refluxed at 165 °C for 120 h. The cooled red solution was poured onto ice (200 cm^3), acidified with 4M hydrochloric acid, and extracted with diethyl ether (3 × 100 cm^3). The combined ethereal extracts were washed with water (2 × 100 cm^3), dried, ($MgSO_4$), and concentrated to provide an orange oil (7.23 g), which, on distillation under reduced pressure, afforded the title compound (**17**) as a colourless liquid, b.p. 68—72 °C/0.2 mmHg (6.0 g, 78%).

Preparation of Methyl 4-Cyano-4-pentafluorophenylhexanoate (**21**).—To a stirred mixture of compound (**17**) (12.0 g, 51.1 mmol) and methyl propenoate (8.6 g, 100 mmol) was added slowly, and with the exclusion of moisture, Triton B (1.0 cm^3). When the initial exothermic reaction had subsided, the pale green mixture was heated on a steam-bath for 5.5 h. The cooled mixture was diluted with trichloromethane (200 cm^3), washed with water (3 × 50 cm^3), dried ($CaCl_2$) and concentrated to give a pale green viscous oil (16.7 g). Distillation of this under reduced pressure in a 15 cm Vigreux column afforded the *title compound* (**21**) as a colourless liquid, b.p. 117—120 °C/0.15 mmHg, which crystallised with time to provide a white solid m.p. 47—49 °C (12.5 g, 76%) (Found: C, 52.3; H, 3.7; F, 30.0; N, 4.2. $C_{14}H_{12}F_5NO_2$ requires C, 52.3; H, 3.7; F, 29.6; N, 4.4%); $\nu_{max.}$ 1 745 (C=O) and 2 250 cm^{-1} (C≡N); δ_H 1.10 (3 H, t, *J* 7 Hz, Me), 2.00 (2 H, q, CH_2), 2.48 (4 H, A_2B_2, CH_2CH_2), and 3.66 (3 H, s, CO_2Me); δ_F 137.6 (2 F, m, 2,6-F), 153.0 (1 F, tt, *J* 22 and 3 Hz, 4-F), and 160.3 (2 F, m, 3,5-F).

Reaction of Methyl 4-Cyano-4-pentafluorophenylhexanoate (**21**) *with Aqueous Sodium Hydroxide*.—A mixture of compound (**21**) (11.0 g, 34.3 mmol) and a solution of sodium hydroxide (1.54 g, 38.5 mmol) in water (20 cm^3) was refluxed for 8 h. The cooled solution was poured onto ice (200 cm^3), when a white waxy solid was precipitated from solution. The mixture was acidified with 4M hydrochloric acid and extracted with diethyl ether (3 × 100 cm^3); the combined ethereal extracts were washed with water (3 × 50 cm^3), dried ($MgSO_4$), and concentrated to provide a pale yellow viscous oil (11.28 g), shown by n.m.r. spectroscopy to contain at least five components. Fractional crystallisation from trichloromethane afforded: (*i*) a white powdery solid, m.p. 188—189 °C, identified as *3-ethyl-3-(2,3,5,6-tetrafluoro-4-hydroxyphenyl)piperidine-2,6-dione* (**24**) (Found: C, 51.1; H, 3.5; F, 25.2; N, 4.5. $C_{13}H_{11}F_4NO_3$ requires C, 51.1; H, 3.6; F, 24.9; N, 4.6%); $\nu_{max.}$ 1 680 and 1 750 (C=O), 3 100, 3 200 (NH), and 2 500—3 440 cm^{-1} (OH); δ_H 1.01 (3 H, t, *J* 7 Hz, Me), 2.21 (2 H, q, CH_2), 1.96—2.80 (5 H, m, CH_2CH_2, OH disappeared in D_2O) and 9.68 (1 H, s, NH disappeared in D_2O); δ_F 140.5 and 162.0 (4 F, AA'XX' system, 2,6-F and 3,5-F), and (*ii*) a complex mixture of products, including 4-cyano-4-pentafluorophenylhexanoic acid (**22**), not investigated further.

Preparation of 4-Cyano-4-pentafluorophenylhexanoic Acid (**22**).—A mixture of methyl 4-cyano-4-pentafluorophenylhexanoate (**21**) (1.0 g, 3.12 mmol) and a solution of sodium hydroxide (0.14 g, 3.50 mmol) in water (1.8 cm^3) was refluxed for 2 h. The cooled homogeneous solution was poured onto ice (20 cm^3) and acidified with 4M hydrochloric acid to form a white precipitate which was extracted into diethyl ether (3 × 25 cm^3). The combined ethereal extracts were washed with water (2 × 20 cm^3), dried ($MgSO_4$), and concentrated to afford a colourless oil (1.03 g) which was crystallised by refrigeration at −20 °C followed by warming to room temperature to give a white solid, m.p. 122—127 °C. Recrystallisation from aqueous ethanol afforded the title compound (**22**) as white needles, m.p. 130—132 °C (0.81 g, 85%); $\nu_{max.}$ 1 720 (C=O), 2.245 (C≡N), and 2 380—3 460 cm^{-1} (acid-OH); δ_H 1.09 (3 H, t, *J* 7 Hz, Me), 1.80 (2 H, m, CH_2), 2.50 (4 H, A_2B_2, CH_2CH_2), and 9.22 (1 H, s, CO_2H disappeared in D_2O); δ_F 138.0 (2 F, m, 2,6-F), 155.0 (1 F, t, *J* 19 Hz, 4-F), and 161.8 (2 F, m, 3,5-F), contaminated with traces of 2,3,5,6-tetrafluoro-4-methoxy- and -4-hydroxyphenyl-containing products.

Preparation of 3-Ethyl-3-pentafluorophenylpiperidine-2,6-dione (**6**).—(*a*) A stirred mixture of 4-cyano-4-pentafluorophenylhexanoic acid (**22**) (0.73, 2.38 mmol), glacial acetic acid (2 cm^3) and concentrated sulphuric acid (0.5 cm^3) was heated at

100 °C for 30 min. The cooled solution was poured onto ice (20 cm^3), neutralised to pH 6 with 4M sodium hydroxide, and the resulting white solid extracted into trichloromethane (3 × 20 cm^3). The combined extracts were washed with 4M sodium hydroxide (2 × 20 cm^3) and water (20 cm^3), dried ($CaCl_2$), and concentrated to provide a white solid (0.40 g). Recrystallisation (twice) from ethyl acetate–light petroleum (b.p. 100—120 °C) afforded the *title compound* (**6**) as white plates, m.p. 105—106 °C (55%) (Found: C, 50.7; H, 3.1; F, 30.6; N, 4.4. $C_{13}H_{10}F_5NO_2$ requires C, 50.8; H, 3.3; F, 30.9; N, 4.6%). $\nu_{max.}$ 1 705, 1 735 (C=O), 3 095, and 3 190 cm^{-1} (NH); *m/z* 307 (M^+), 292 ($M^+ - Me$), 279 ($M^+ - C_2H_4$), 262 ($M^+ - CONH - H_2$), 251 (M^+, $- C_2H_4 - CO$), 250 ($M^+ - C_2H_5 - CO$), 236 ($M^+ - C_2H_4 - HCNO$), 222 ($M^+ - HCNO - CH_2CO$), and 207 (base peak, $M^+ - HNCO - CH_2CO - Me$); δ_H 1.04 (3 H, t, *J* 7 Hz, Me), 1.98—3.11 (6 H, complex, CH_2, CH_2CH_2), and 9.10 (1 H, s, NH disappeared in D_2O); δ_F 137.4 (2 F, m, 2,6-F), 154.6 (1 F, t, *J* 21 Hz, 4-F), and 161.1 (2 F, m, 3,5-F).

(*b*) A stirred solution of methyl 4-cyano-4-pentafluorophenylhexanoate (**21**) (7.0 g, 21.8 mmol), glacial acetic acid (21 cm^3), and concentrated sulphuric acid (5.25 cm^3) was heated at 100 °C for 2 h. The cooled pale yellow solution was poured onto ice (150 cm^3), when a white solid precipitated out. The whole was neutralised to pH 7 with 4M sodium hydroxide, and the white crystalline solid was filtered off at the pump, washed thoroughly with cold water, and dried *in vacuo*, it was identified as the title compound (**6**), m.p. 105—106 °C (6.32 g, 94%).

Reaction of 3-*Ethyl*-3-*pentafluorophenylpiperidine*-2,6-*dione* (**6**) *with Aqueous Ethanolic Ammonia*.—A mixture of compound (**6**) (1.0 g, 3.25 mmol), concentrated aqueous ammonia (*d* 0.088 g cm^{-3}; 1.25 cm^3, 10 mmol) and absolute ethanol (2.5 cm^3) was shaken and heated at 120 °C in a Carius tube for 24 h. The cooled dark red product was poured into water (20 cm^3) and extracted with dichloromethane (3 × 20 cm^3); the combined dichloromethane extracts were washed with water (20 cm^3), dried ($CaCl_2$), and concentrated to provide an orange oil (0.20 g). N.m.r. spectroscopy showed four main components, with a 4-amino-2,3,5,6-tetrafluorophenyl-containing compound as the major product but with at least two less abundant pentafluorophenyl-containing compounds.

The brown aqueous residue was acidified with 4M hydrochloric acid, extracted with diethyl ether (3 × 30 cm^3), and the extract dried ($MgSO_4$) and concentrated to provide a yellow oil which crystallised with time to give an off-white solid (0.38 g). Adsorption chromatography [10 g column eluted with chloroform–methanol (90:10)] gave: (*i*) R_F 0.57, unidentified (0.04 g), (*ii*) R_F 0.49, unidentified (0.03 g), and (*iii*) R_F 0.41, white solid, identified as 4-*carboxamido*-4-*pentafluorophenylhexanoic acid* (**23**), m.p. 144—146 °C (0.17 g, 16%) (Found: C, 48.2; H, 3.8; F, 29.0; N, 4.3. $C_{13}H_{12}F_5NO_3$ requires C, 48.0; H, 3.7; F, 29.2; N, 4.3%); $\nu_{max.}$ 1 650 (C=O), 1 710 (C=O), 3 190, 3 420 (NH), 2 380—3 500 cm^{-1} (OH); *m/z* 307 ($M^+ - H_2O$), 292 ($M^+ - H_2O - Me$), 279 ($M^+ - H_2O - C_2H_4$), 262 ($M^+ - H_2O - HNCO - H_2$), 251 ($M^+ - H_2O - C_2H_4 - CO$), 250 ($M^+ - H_2O - C_2H_5 - CO$), 222 ($M^+ - H_2O - HNCO - CH_2CO$), and 207 (base peak, $M^+ - H_2O - HNCO - CH_2CO - Me$); δ_H 0.88 (3 H, t, *J* 7 Hz, Me), 1.80—2.68 (6 H, m, $- CH_2CH_2$, CH_2), and 6.87 (2 H, s, NH_2 disappeared in D_2O); δ_F 136.5 (2 F, m, 2,6-F), 157.8 (1 F, t, *J* 20 Hz, 4-F), and 163.9 (2 F, m, 3,5-F), and (*iv*) R_F 0.22, yellow oil, unidentified (0.10 g).

Reaction of Methyl 4-*Cyano*-4-*pentafluorophenylhexanoate* (**21**) *with Aqueous Ethanolic Ammonia*.—A mixture of compound (**21**) (1.0 g, 3.12 mmol), concentrated aqueous ammonia (*d* 0.880 g cm^{-3}; 7.8 cm^{-3}, 62.4 mmol) and absolute ethanol (5 cm^3) was shaken and heated at 100 °C in a Carius tube for 67 h. The cooled orange solution was neutralised to pH 7 with 4M hydrochloric acid, when a white cloudiness was *just* observable. The mixture was extracted with diethyl ether (3 × 50 cm^3), the combined ethereal extracts were washed with water (50 cm^3), dried ($MgSO_4$), and concentrated to afford a foamy white solid (0.78 g), Adsorption chromatography [25 g column eluted with trichloromethane–methanol (9:1)] gave: (*i*) R_F 0.36, unidentified (0.01 g), (*ii*) R_F 0.31, unidentified (0.01 g), and (*iii*) R_F 0.26, tentatively identified as 4-(4-amino-2,3,5,6-tetrafluorophenyl)-4-cyanohexanoic acid (**25**) (0.31 g, 29%); $\nu_{max.}$ 1 720 (C=O), 2 260 (C≡N), 1 980—3 520 (OH), and 3 360—3 460 cm^{-1} (NH); δ_H 1.07 (3 H, t, *J* 7 Hz, Me), 1.70—2.90 (6 H, m, CH_2CH_2, CH_2), 6.25 (2 H, s, NH_2); δ_F 141.6 and 160.8 (4 F, AA′XX′ system, 2,6-F and 3,5-F).

Preparation of 3-(4-*Amino*-2,3,5,6-*tetrafluorophenyl*)-3-*ethylpiperidine*-2,6-*dione* (**4**).—A mixture of the crude product obtained from the amination of methyl 4-cyano-4-pentafluorophenylhexanoate (**21**) (0.88 g), glacial acetic acid (5 cm^3), and concentrated sulphuric acid (1.27 cm^3) was refluxed at 165 °C for 16 h. The cooled, dark red solution was poured onto ice (30 cm^3) and scratched to afford a white gluey solid which was extracted into diethyl ether (3 × 30 cm^3). The combined ethereal extracts were washed with 10% aqueous sodium hydrogen carbonate (2 × 30 cm^3) and water (30 cm^3), dried ($MgSO_4$) and concentrated to provide a white solid, m.p. 54—98 °C (0.57 g). Adsorption chromatography on a 0.37 g portion (20 g column eluted with trichloromethane–acetone (95:5) gave: (*i*) R_F 0.57, unidentified (0.01 g), (*ii*) R_F 0.47, a white solid, the *title compound* (**4**) [0.11 g, 16% from methyl 4-cyano-4-pentafluorophenylhexanoate (**21**)]. Recrystallisation from trichloromethane–light petroleum (b.p. 40—60 °C) afforded white crystals (0.06 g), m.p. 138—139 °C (Found: C, 51.4; H, 4.0; F, 25.0; N, 9.2. $C_{13}H_{12}F_4N_2O_2$ requires C, 51.3; H, 3.9; F, 25.0; N, 9.2%); $\nu_{max.}$ 1 670, 1 710 (C=O), 3 110, 3 220 (CONH) and 3 350, 3 460 cm^{-1} (NH); *m/z* 304 (base peak, M^+), 289 ($M^+ - Me$), 276 ($M^+ - C_2H_4$), 275 ($M^+ - C_2H_5$), 247 ($M^+ - C_2H_5 - CO$), 219 ($M^+ - HNCO - CH_2CO$), 204 ($M^+ - HNCO - CH_2CO - Me$) and 190 ($M^+ - HNCO - CH_2CO - C_2H_5$); δ_H 1.01 (3 H, t, *J* 7 Hz, Me), 2.19 (2 H, q, *J* 7 Hz, CH_2), 1.94—2.80 (4 H, complex, CH_2CH_2), 4.13 (2 H, s, NH_2 disappeared in D_2O) and 8.41 (1 H, s, NH disappeared in D_2O); δ_F 140.3 and 160.7 (4 F, AA′XX′ system, 2,6-F and 3,5-F), (*iii*) R_F 0.30, a white solid, m.p. 221—222 °C, unidentified (0.10 g), and (*iv*) R_F 0.11. a colourless oil, unidentified (0.08 g).

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