Derivation of Fluorine-Containing Pyridine Dicarboxylates IV. *N*-Substituted Dihydropyridine Derivatives [1]

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Received April 16, 1990

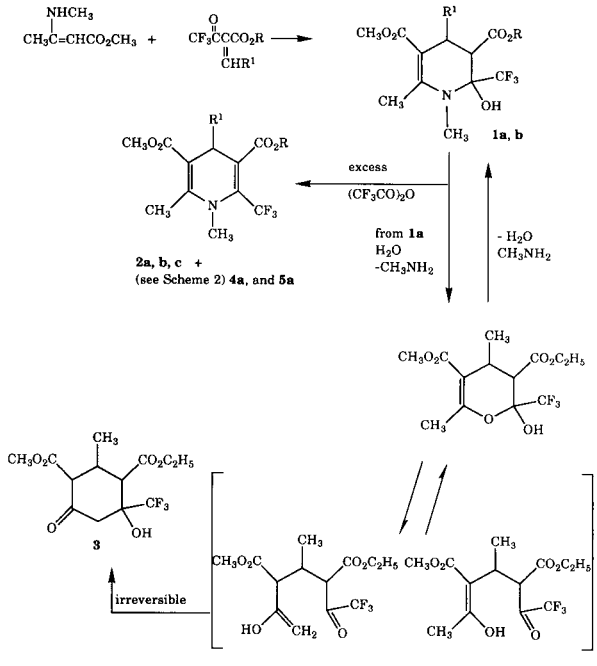
The bio-activity observed for certain Hantzsch derived fluorine-containing dihydropyridinecarboxylates **6**, **11** and **12** and pyridinecarboxylates **10** prompted the preparation of a number of related *N*-substituted dihydropyridines for the first time. One method involved a mixed Hantzsch sequence to give **2** from which unexpected side products **3-5** were also isolated and identified. A second preparative method relied on lithio-base deprotonation of **6**, **11** and **12** followed by alkylation or acylation to give products **7-9** and **13-15**. Structure determination and stereo-assignments are discussed in terms of their spectral properties, and reaction mode.

J. Heterocyclic Chem., **27**, 1697 (1990).

It is known that pyridine calcium antagonists used to combat hypertension, such as nefidepine, are much more active as the 1,4-dihydro species than as fully aromatized pyridines [2] Further, these dihydropyridines are best when saturated only with hydrogen; N-alkyl 1,4-dihydropyridines are less effective inhibitors than the N-H variety. More recently other pyridines, similarly derived from Hantzsch reaction sequences, but containing 2,6-polyfluoroalkyl substitution, have been shown to exhibit desirable herbicide activity [3]. SAR studies have revealed that these materials are most active as the fully aromatized pyridines, although the corresponding (1,4), (3,4), (1,2), and (1,6) dihydropyridines [4] also have notable activity. It could be argued that these dihydropyridines are freely inter-convertible, including *in vivo* oxidation to pyridines. Consequently it became desirable for purposes of SAR and mode-of-action studies to prepare the corresponding *N*-substituted dihydropyridines. Since the desired candidates are unknown [5], new methodologies as reported herein were devised for their synthesis.

Initially, pause was given to contacting the fluorine-containing dihydro 3,5-pyridinedicarboxylates derived *via* the Hantzsch (*i.e.* **6**, **11** and **12**), to base induced alkylation, the usual method employed to derive *N*-substituted dihydropyridines [5]. This was due to their known sensitivity to base, particularly strong amines, in effecting their transformation *via* hydrogen fluoride elimination, to the novel 2-(difluoromethyl)pyridines [3]. Consequently, as shown in Scheme 1, a mixed Hantzsch reaction was employed to produce candidates **2a-c** wherein the desired *N*-methyl substitution was originally implanted in the starting enamino ester [6]. The initial hydrates **1** were dehydrated by reflux with trifluoroacetic anhydride. Two side reactions were noted in these transformations; one is illustrated in Scheme 1, while the other is shown with scope expansion in Scheme 2. Formation of **3** (structure confirmed by single cyrstal X-ray) is postulated to arise by irreversible formation from hydroxydihydropyran (this last intermediate is encountered in Hantzsch sequences wherein ammonia is introduced after the initial condensation of trifluoromethyl acetoacetic esters and aldehyde [3]). This would explain the effectiveness of the terminal methyl group in competing somewhat (through its enol as shown), with the more prevalent conjugated enolic oxygen as a nucleophilic source for ring closure on the electrophilic trifluoromethyl carbonyl.

Scheme 1

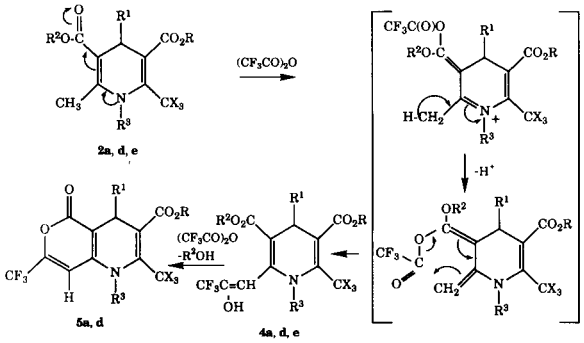


a, R= C_2H_5, R^1 = CH_3; b, R= CH_3, R^1= C_2H_5; c, R= CH_3, R^1= $CH_2CH(CH_3)_2$

The secondary products isolated along with **2a** were shown to arise by further reaction of **2** with trifluoroacetic anhydride, first forming the acyclic acylation product **4**, then the fused pyrone **5**. This unique reaction could be expanded as shown in Scheme 2 to *N*-hydrogen dihydropyridines, including those having 2,6-dimethyl groups. On the other hand, substitution of acetic anhydride for trifluoroacetic anhydride failed to produce the reaction

even at much elevated temperatures. Likewise, the corresponding fully aromatized pyridines with either 2 or 4 methyl substitution failed to react with trifluoroacetic anhydride. The propensity for this latter reagent to acylate 2-methyl-1,4-dihydropyridines may be due to the better charge delocalization outside the ring in this species compared with pyridines. As shown in Scheme 2, a mechanism can be written for formation of **4** wherein the hetero nitrogen activates the ester carbonyl for initial *O*-acylation, followed by trifluoroacetyl rearrangement (approximating a 1,5-sigmatropic shift) to the enolized 2-methyl moiety *via* an intermediate having exo double bonds at the 2 and 3 position. Further, this mechanism appears quite different from what occurs in previously reported substitutions onto 2,6-dialkyl groups in 1,4-dihydro-3,5-pyridinedicarboxylates [7,8].

Scheme 2

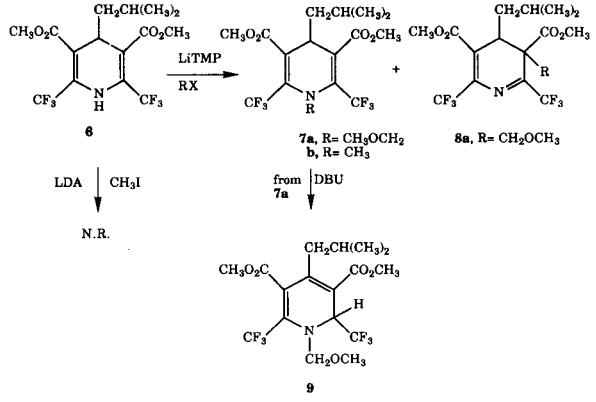


a, R= C_2H_5, R^1, R^2, R^3= CH_3, X= F
d, R, R^2= C_2H_5, R^1= CH_3, R^3= H, X= F
e, R, R^2= CH_3, R^1= C_2H_5, R^3= H, X= H

Access to *N*-substituted dihydropyridines wherein the 2 and 6 positions are *both* substituted with bio-optimal poly or perfluoromethyl groups is quite difficult by the mixed Hantzsch reaction as typified by Scheme 1. The requisite enamine and alkylidene portions of tri(di)fluoroacetoacetic ester do not easily add, Michael-wise, in the initial step [9], nor is the former derivative easily capable, without complications of much *N*-substitution beyond simple alkyl. However, as mentioned earlier, the 1,4; 1,2 and 1,6 dihydro(dihydrogen)-3,5-pyridinedicarboxylates are known to be base sensitive, eliminating hydrogen fluoride in novel fashion to form pyridines [3]. Nevertheless, as described below, materials **6**, **10**, **11** and **12** were converted to anions *via* metallic bases, and thence by reaction with electrophiles, to substituted dihydropyridines. It is in fact remarkable that in none of the studies reported below were there even trace amounts of dehydrofluorination products discerned, even though often detailed glc/ms measurements were carried out on crude reaction mixtures.

Initially the studies employed purified 1,4-dihydro-3,5-pyridinedicarboxylates, **6**, obtained from a symmetrical Hantzsch reaction from 2 molar equivalents of trifluoroacetoacetic ester and isovaleraldehyde [3]. As can be seen from Scheme 3, lithium diisopropylamide (LDA) was not appropriate and starting material was recovered. Lithium tetramethylpiperidine (TMP) however, proved equal to the task, probably because this base or the conjugate amine is resistant to alkylation, allowing hindered **6** to undergo reaction with methyl iodide and bromomethyl methyl ether. The major product was **7**, accompanied by minor amounts of **8** (**8a** was isolated and characterized). The latter isomer undoubtedly arises from the ambient nature of the dihydropyridyl anion distributing its charge between the 1 and 3 positions. Structure conformation for **7a,b** is based on nmr. Thus the ^1H spectra clearly define methyl and methylene respectively attached to nitrogen, from their downfield absorptions. Important also is the lack of prochiral properties for the 4-isobutyl *methyl* groups or *N*-methoxy*methylene* protons; they are characterized by a simple doublet and singlet respectively as would be expected for these symmertrical compounds. Similarly the 2,6-trifluoromethyl moieties in the ^{19}F nmr are identical. In contrast the 1,2 and 3,4 dihydro isomers (**9** and **8a** respectively) are necessarily diastereotopic, and thus give prochiral centers leading to AB quartets and pairs of doublets for the 1 or 3-CH_3OCH_2 and 4-$(CH_3)_2CHCH_2$ moieties. The structure of **9** is further confirmed by the characteristic N-CH_2O absorption, and characteristic vicinal coupling of proton with one, but not both trifluoromethyl groups. Chemical shift clearly indicates material **8a** has the methoxymethyl group attached to carbon rather than nitrogen. Moreover, attachment at C-3 is confirmed by high field proton decoupling experiments between the 4-proton and isobutylmethylene group.

Scheme 3

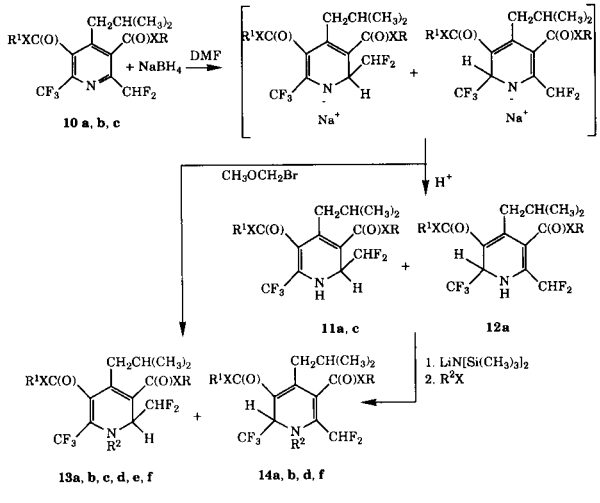


Conversion of **7a** to **9** is effected by 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), a result paralleled by similar *N*-hydrogen 1,4-dihydrospecies under basic [3], or acidic conditions [10]. But **9** was not formed from **7a** when treated by metallic (irreversible?) bases such as methoxide or lithium TMP. Apparently the tertiary amine functions

as a reversible acid-base to promote tautomerism; presumably this lack of proton donation by conjugate acids of the stronger bases (*i.e.* methanol, or secondary amines) obviates this transformation. Attempts to likewise isomerize conjugated diene **8a** failed, illustrating the thermodynamic driving force for **7** to **9** includes undoubtedly a strong component for conjugation.

Next, attention was focused on 1,2 and 1,6-dihydropyridines derived from sodium borohydride reduction of 2-(difluoromethyl)-6-(trifloromethyl)-3,5-pyridinedicarboxylates, **10** [3]. After alkylation, *N*-substitution resulted, with formation of isomeric mixtures of 1,2 and 1,6-dihydropyridines, **13** and **14**. Although initially pyridine **10** was contacted with sodium borohydride in dimethyl formamide (**WARNING-HAZARDOUS MIXTURE**), followed by alkylating agent, it was found more convenient to first prepare dihydropyridines **11** and **12**, then contact them successively with lithium bis(trimethylsilyl)amide and alkylating agent (Scheme 4).

Scheme 4

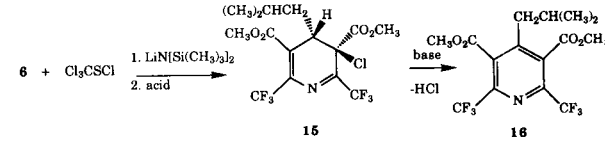


a, RX, R^1X= CH_3O, R^2= CH_3OCH_2
b, RX, R^1X= CH_3S, R^2= CH_3OCH_2
c, RX= CH_3O, R^1X= 1-Pyrazolyl, R^2= CH3
d, RX, R^1X= CH_3O, R^2= CH_3
e, RX, R^1X= CH_3O, R^2= $ClCH_2C(O)$-
f, RX, R^1X= CH_3O, R^2= Cl_3CS

Little or no interconversion between 1,2 and 1,6-dihydro isomers occurred during the transformations. Thus the ratio of reactant **11** and **12** (easily determined by examination of the contrasting multiplets characteristic of their ^{19}F nmr) was identical with the product ratio of **13** and **14** respectively. Likewise, when pure isomer **11c** was used as substrate only corresponding **13c** resulted as product.

Attention then turned to reaction of anions from **6**, **11** and **12** by acid derivatives. The contrast in properties between trifluoromethyl and difluoromethyl is shown when a mixture of **11a** and **12a** was chloroacetylated. Despite recharges of lithium base and chloroacetyl chloride only the 1,2 isomer, *i.e.* **11a** successfully gave product **13e**. On the other hand the same mixture of **11a** and **12a** with perchloromethyl mercaptan gave both isomeric products; moreover they were separable by hplc, and Kugelrohr distillation into pure **13f** and **14f**. In a similar reaction with substrate **6**, chlorination at the 3 position rather than *N*-sulfenation occurred (Scheme 5). Curiously, the single diastereomer **15** formed is stable enough to survive work-up and even Kugelrohr distillation, although it is easily dehydrochlorinated to pyridine **16** [3] by base. This contrast in properties arises presumably from its spatial structure (as determined by single crystal X-ray determination). Material **15** has hydrogen *cis* to chlorine with the former atom in quasi-equitorial configuration and the chlorine atom axial. This would appear qualitatively to be both the kinetic and thermodynamically preferred conformer. Thus the large perchloromethylmercaptan molecule would be expected to approach the 3 carbon *trans* to the large 4-isobutyl group (kinetic). A final axial position of the isobutyl group would appear to lessen steric crowding with the adjacent 5-carboxyl group while minimizing interaction with the quasi-axial 3-carboxyl group (thermodynamic). The *cis* orientation of hydrogen and chlorine would inhibit spontaneous hydrogen chloride expulsion, necessitating base to racemize this isomer for ready *trans* elimination to aromatic **16**.

Scheme 5



EXPERIMENTAL

All melting points were determined on a Laboratory Devices Mel-Temp apparatus and are uncorrected. ^1H, ^{13}C and ^{19}F nmr spectra were recorded on a Varian EM-360-L (60 MHz), XL300 (300 MHz), or XL400 (400 MHz) instruments referenced to tetramethylsilane and fluorotrichloromethane respectively. Exact ^{19}F chemical shifts were not always recorded, although they were usually in the regions found for CF_3 (-65 ppm) and CHF_2 (-115 ppm); rather emphasis was given to number and type of multiplicity to confirm sample identify and purity. Mass spectra were measured by a Varian CH7 mass spectrometer with electron ionization (e.i.) or isobutane chemical ionization (ci) expressed as molecular weight (m/e). Liquid chromatography purification was achieved on a Waters Prep LC, model 500A, with refractive index detector (hplc), or by Chromatotron (rotary tlc). Unless otherwise noted, bp's are recorded as oven temperatures during bulb-to-bulb (Kugelrohr) distillations. All microanalyses were performed by Atlantic Microlab Inc., Norcross, Georgia 30091. The preparation and characterization of materials **6**, **10a,b,c**, **11a**, **12a** and **16** have been previously reported [3], and will not be repeated here.

3-Ethyl 5-Methyl 1,2,3,4-Tetrahydro-2-hydroxy-1,4,6-trimethyl-2-(trifluoromethyl)-3,5-pyridinedicarboxylate (**1a**).

Ethyl 2-trifluoroacetyl-2-butenoate [3] (1.94 g, 8.6 mmoles) was dissolved in 10 ml of carbon tetrachloride with 1.3 g (10 mmoles) of methyl 3-(methylamino)crotonate [11] and the solution permitted to stand overnight. After solvent removal the residue was subjected to hplc with 3.5% ethyl acetate in cyclohexane to give fraction 3, which was recrystallized from hexane, mp 105-106°, 1.5 g (51%); ^{1}H nmr (deuteriochloroform): δ 1.09 (d, 3H, 4-CH_3), 1.25 (t, 3H, CH_2CH_3), 2.3 (s, 3H, 6-CH_3), 2.95 (q, 3H, NCH_3 coupled to CF_3), 3.1 (m's, 2H, 3-H, 4-H), 3.6 (s, 3H, OCH_3), 4.2 (q, 2H, OCH_2), 7.3 (s, 1H, OH); ^{19}F nmr (q, CF_3 coupled to NCH_3); ms: glc/ci m/e 339.

Anal. Calcd. for $C_{14}H_{20}F_3NO_5$: C, 49.56; H, 5.94; N, 4.13. Found: C, 49.52; H, 5.95; N, 4.05.

Dimethyl 4-Ethyl-1,2,3,4-tetrahydro-2-hydroxy-1,6-dimethyl-2-(trifluoromethyl)-3,5-pyridinedicarboxylate (**1b**).

To 200 ml of methylene chloride containing 0.5 ml of piperidine and 170 g (1.0 mole) of methyl trifluoroacetoacetate was added 75 g (1.3 moles) of propionaldehyde. Exterior cooling was used to maintain the temperature below 35°. The mixture was stirred for 24 hours, then solvent was removed under vacuum to give 201 g of crude. The material was distilled through a 2 foot vigreux column to give methyl 2-trifluoroacetyl-2-pentenoate at 68° (25 mm Hg) as a mixture of isomers, which was used for further synthesis; ^{1}H nmr (deuteriochloroform): δ 1.2 (2 t, 3H, CH_2CH_3), 2.5 (m, 2H, CH_2CH_3), 3.8 (2s, 3H, OCH_3), 7.4 (t, 1H, $CHCH_2$).

Methyl 2-trifluoroacetyl-2-pentenoate (2.1 g, 10 mmoles) was dissolved in 20 ml of carbon tetrachloride with 1.3 g (10 mmoles) of methyl 3-(methylamino)crotonate [11]. After solvent removal, the residual 3.2 g was dissolved in hexane, cooled and crystallization allowed to occur. The solid was separated, dried on a porous plate, then recrystallized from hexane, mp 79-80°. In another preparation, 11.7 g (86%) was similarly, obtained; ^{1}H nmr (deuteriochloroform): δ 0.8 (t, 3H, CH_2CH_3), 1.5 (m, 2H, CH_2CH_3), 2.5 (s, 3H, 6-CH_3), 3.1 (q, 3H, NCH_3 coupled to CF_3), 3.75 and 3.9 (2s, 6H, 2 OCH_3), 7.4 (s, 1H, OH), 3-H and 4-H as multiplets obscured by baseline between 1.2-4.5; ^{19}F nmr (closely spaced q, CF_3 coupled to CH_3).

Anal. Calcd. for $C_{14}H_{20}F_3NO_5$: C, 49.56; H, 5.94; N, 4.13. Found: C, 49.49; H, 5.94; N, 4.08.

5-Ethyl 3-Methyl 1,4-Dihydro-1,2,4-trimethyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**2a**).

Ethyl 2-(trifluoroacetyl)-2-butenoate [3] (4.2 g, 19 mmoles) was added to an equimolar amount of methyl 3-(methylamino)crotonate [11] in 50 ml of carbon tetrachloride, and permitted to stir 2 hours. The solvent was removed to give 6.9 g of crude which was recrystallized from hexane by standing over a weekend in the refrigerator to give 3.8 g. All but 0.3 g of this material was dissolved in methylene chloride and 3.5 g of trifluoroacetic anhydride was added with reflux for 1 hour. The cooled solution was washed with sodium bicarbonate solution, vacuum treated to remove solvent and the residue eluted by hplc with 8 l of 3.3% ethyl acetate in cyclohexane to which had been added 3 ml of acetic acid. The title compound was contained fractions 4-6. Kugelohr distillation gave bp 130-140° (0.3 mm Hg), 1.0 g (16%); ^{1}H nmr (deuteriochloroform): δ 1.05 (d, 3H, 4-CH_3), 1.35 (t, 3H, CH_2CH_3), 2.5 (s, 3H, 2-CH_3), 3.3 (q, 3H, NCH_3 coupled to CF_3), 3.8 (s, 3H, OCH_3), 3.8 (q, 1H, 4-H), 4.4 (q, 2H, CH_2CH_3); ms: glc/ci m/e 321.

Anal. Calcd. for $C_{14}H_{18}F_3NO_4$: C, 52.34; H, 5.65; N, 4.36. Found: C, 52.15; H, 5.63; N, 4.34.

Dimethyl 4-Ethyl-1,4-dihydro-1,6-dimethyl-2-(trifluoromethyl)-3,5-pyridinedicarboxylate (**2b**).

Crude **1b** (6 g, 17.7 mmoles) was placed in 30 ml of methylene chloride and to this was added 6 g of trifluoracetic anhydride. The material was allowed to reflux for 2 hours, then the reaction mixture was treated with sodium bicarbonate solution, and water washed after methylene chloride extraction. After solvent evaporation the crude was eluted though a single hplc column using 8 l of 97.3% cyclohexane, 2.7% ethyl acetate containing 30 ml of acetic acid. Fractions 2-4 were collected as product with some mechanical loss occurring. After Kugelrohr distillation at 120-160° (1 mm Hg), 0.9 g (16%) product was collected as yellow oil; ^{1}H nmr (deuteriochloroform): δ 0.8 (t, 3H, CH_2CH_3), 1.3 (m, 2H, CH_2CH_3), 2.4 (s, 3H, 6-CH_3), 3.1 (q, 3H, NCH_3 coupled to CF_3), 3.6 and 3.7 (2s, 6H, OCH_3), 3.75 (m, 1H, 4-H); ^{19}F nmr (q, CF_3 coupled to CH_3).

Anal. Calcd. for $C_{14}H_{18}F_3NO_4$: C, 52.34; H, 5.65; N, 4.36. Found: C, 52.58; H, 5.74; N, 4.12.

Dimethyl 1,4-Dihydro-1,2-dimethyl-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**2c**).

To a cooled (ice bath) solution of methyl 4,4,4-trifluoroacetoacetate (64.3 g, 0.27 mole) and isovaleraldehyde (47 g, 0.547 mole) in 35 ml of ether was added 0.5 ml of piperidine. The ensuing reaction was exothermic, with the temperature controlled by an ice bath. After the exotherm had subsided, the bath was removed and the mixture stirred at ambient temperature for 2 hours. The reaction mixture was then cooled in an ice bath and 10 g of trifluoroacetic anhydride was added, keeping the temperature below 30°. The resulting mixture was then filtered, volatiles removed *via* a rotary evaporator and the residue distilled at 80 mm Hg through a 24 inch Vigreux column, with final pressure reduced to 4 mm Hg when vapor temperature reached 60°. Methyl 5-methyl-2-(trifluoroacetyl)-2-hexenoate was obtained as 27 g (42%) of colorless liquid, bp 75-77° (4 mm Hg).

In a small volume of carbon tetrachloride in a 50 ml flask was placed methyl 5-methyl-2-(trifluoroacetyl)-2-hexenoate (12 g, 40 mmoles, 80% assay) and 5.2 g (40 mmoles) of methyl 3-(methylamino)crotonate. The mixture was permitted to stand 12 days, whereupon solvent was removed by vacuum treatment to 75° (1 mm Hg) to give 15.3 g. A portion (10 g) of this crude was dissolved in 50 ml of methylene chloride with 10 g of trifluoroacetic anhydride and refluxed 2 hours. After removing volatiles on a rotary evaporator the residue was Kugelrohr distilled to give 11.2 g. This was subjected to hplc (2.8% ethyl acetate in cyclohexane). Fractions 8-11 contained product, which after Kugelrohr distillation at 125-130° (0.5 mm Hg) gave 2.1 g (22%) of yellow oil having 100% glc assay, n_D^{23} 1.4769; ^{1}H nmr (deuteriochloroform): δ 0.8 (d, 6H, $CH(CH_3)_2$), 1.2 (d, 2H, CH_2), 1.3 (m, 1H, $CH(CH_3)_2$), 2.38 (s, 3H, 2-CH_3), 3.15 (q, 3H, NCH_3 coupled to CF_3), 3.65 and 3.75 (2s, 6H, OCH_3), 3.7 (m, 1H, 4-H); ^{19}F nmr (closely spaced q, CF_3 coupled to NCH_3).

Anal. Calcd. for $C_{16}H_{22}F_3NO_4$: C, 55.01; H, 6.35; N, 4.01. Found: C, 55.01; H, 6.32; N, 3.76.

Diethyl 1,4-Dihydro-2,4-dimethyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**2d**).

A mixture of 184 g (1.0 mole) of ethyl 4,4,4-trifluoroacetate, ethyl 3-aminocrotonate (129 g, 1.0 mole), acetaldehyde (44 g, 1.0 mole) and triethyl amine (1.0 g, 0.01 mole) was stirred in 100 ml

of ethanol and the temperature allowed to rise from the exotherm until reflux attained. Thereafter reflux was maintained for 2 hours, then the mixture was cooled and concentrated on a rotary evaporator. The residue was taken up in 700 ml of methylene chloride and washed with 500 ml of 1% hydrochloric acid, followed by 250 ml of 10% sodium chloride. The washed solution was dried over magnesium sulfate, filtered and concentrated. To a stirred solution of 0.66 mole of this crude material in 200 ml of methylene chloride was added 102 ml (0.73 mole) of trifluoroacetic anhydride. The mixture was stirred at room temperature for 2 hours, then washed twice with 300 ml of water, the organic phase dried over magnesium sulfate, filtered and concentrated on a rotary evaporator. Kugelrohr distillation afforded 190 g of product, bp 140-150° (0.5 mm Hg). Purification of 15 g by silica gel hplc using 5% ethyl acetate in cyclohexane followed by Kugelrohr distillation at 110-125° (0.2 mm Hg) gave 8.7 g (51%) yellow oil, n_D^{25} 1.4859; ^{1}H nmr (deuteriochloroform): δ 1.2 (m's, 9H, 2 CH_2CH_3 and 4-CH_3), 2.32 (s, 3H, 2-CH_3), 3.8 (q, 1H, 4-H), 4.12 and 4.16 (2q, 4H, 2 CH_2CH_3), 6.3 (b, 1H, NH); ^{19}F nmr δ -64.06 (s, CF_3).

Anal. Calcd. for $C_{14}H_{18}F_3NO_4$: C, 52.34; H, 5.65; N, 4.36. Found: C, 52.57; H, 5.71; N, 4.14.

Dimethyl 1,4-Dihydro-2,6-dimethyl-4-ethyl-3,5-pyridinedicarboxylate (**2e**).

To 3 l of 10% aqueous ammonium carbonate were added rapidly 90 ml (1.25 moles) of propionaldehyde and 270 ml (2.50 mmoles) of methyl acetoacetate. The mixture was stirred at room temperature for 2 days, then 300 ml of methylene chloride was added, and the organic layer separated. Solvent removal on a rotary evaporator gave 260 g (82%) of crude solid product. Recrystallization of a portion from 50% v/v ethyl acetate in cyclohexane afforded crystals, mp 144-146°; ^{1}H nmr (deuteriochloroform): δ 0.81 (t, 3H, CH_2CH_3), 1.25 (m, 2H, CH_2CH_3), 2.28 (s, 6H, 2,6-CH_3), 3.80 (s, 6H, OCH_3), 3.95 (t, 1H, 4-H).

Anal. Calcd. for $C_{13}H_{19}NO_4$: C, 61.66; H, 7.51; N, 5.53. Found: C, 61.66; H, 7.59; N, 5.52.

3-Ethyl 1-Methyl 4-Hydroxy-2-methyl-6-oxo-4-(trifluoromethyl)-cyclohexane-1,3-dicarboxylate (**3**).

The hplc fractions 7-9 from **1a** were recrystallized from methylcyclohexane, mp 122-123°; ^{1}H nmr (deuteriochloroform): δ 1.0 (m, 3H, 2-CH_3), 1.3 (t, 3H, CH_2CH_3), 2.3-3.3 (m's, 5H, unassigned), 3.78 (s, 3H, OCH_3), 4.25 (q, 2H, CH_2CH_3), 4.67 (d, 1H, unassigned); X-ray crystal structure for **3**: $C_{13}H_{17}F_3O_6$, monoclinic, space group: P2(1)/C (No. 14) with a = 9.807(3)A, b = 14.910(4)A, c = 10.342(2)A; B = 95.02(2)°, V = 1506A^3, Z = 4; R_1 = 0.0423, R_w = 0.0488.

Anal. Calcd. for $C_{13}H_{17}F_3O_6$: C, 47.86; H, 5.25. Found: C, 47.74; H, 5.20.

5-Ethyl 3-Methyl 1,4-Dihydro-1,4-dimethyl-2-(3,3,3-trifluoro-2-hydroxy-1-propenyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**4a**).

Material **2a** (0.44 g, 1.4 mmoles) was refluxed with 3 g of trifluoroacetic anhydride, the reaction monitored by ^{19}F nmr. After 2 hours all **2a** had reacted. The mixture was vacuum treated to remove volatiles, then the residue was taken up in methylene chloride and washed once with sodium bicarbonate solution. After removal of organic solvent the 0.4 g residue was separated by Chromatotron (4% ethyl acetate in 96% cyclohexane containing a few drops of acetic acid). Fraction 2 (60 mg, 10%) contained **4a** at 84% assay be glc; ^{1}H nmr (deuteriochloroform): δ 1.02 (d, 3H, 4-CH_3), 1.3 (t, 3H, CH_2CH_3), 3.3 (q, 3H, NCH_3), 3.78 (s, 3H, OCH_3), 4.3 (q, 2H, OCH_2CH_3), 5.3 (m, 1H, =CH), 5.9 (s, 1H, OH), 4-H quartet obscured; ^{19}F nmr, (s, and closely spaced quartet, 2-CF_3); ms: glc/ci m/e 417.

Diethyl 1,4-Dihydro-4-methyl-2-(3,3,3-trifluoro-2-hydroxy-1-propenyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**4d**).

Material **2d** (4 g, 6.2 mmoles) was refluxed with 10 ml of trifluoroacetic anhydride for 3 hours. The material was vacuum treated, taken up in methylene chloride and washed once with sodium bicarbonate solution followed by a water wash. The residue deposited solid, which was recrystallized from toluene to give **5d** (see below). The filtrate was evaporated and then subjected to hplc (3% ethyl acetate in cyclohexane containing a few drops of acetic acid) with **4d** eluting as an oil in fractions 3-5. This material was Kugelrohr distilled at 120-130° (0.15 mm Hg) to give 1.0 g (37%), n_D^{22} 1.4850; ^{1}H nmr (deuteriochloroform): δ *ca* 1.25 (2t, 6H, CH_2CH_3), 1.25 (d, 3H, 4-CH_3), 3.1-3.4 (m's, 2H, 4-H and OH), 4.13 and 4.18 (2q, 4H, OCH_2CH_3), 5.7 (s, 1H, =CH), 11.68 (broad, 1H, NH); ^{19}F nmr (2s, equal intensity, CF_3); ms: glc/ci m/e 417.

Anal. Calcd. for $C_{16}H_{17}F_6NO_5$: C, 46.05; H, 4.11; N, 3.36. Found: C, 46.21; H, 4.20; N, 3.25.

Dimethyl 4-Ethyl-1,4-dihydro-2-methyl-6-(3,3,3-trifluoro-2-hydroxy-1-propenyl)-3,5-pyridinedicarboxylate (**4e**).

Material **2e** (4.12 g, 16.3 mmoles) was refluxed in 20 ml of trifluoroacetic anhydride under nitrogen. The solid gradually went into solution which turned red. Both glc and nmr verified disappearance of starting material. The solvent medium was removed by vacuum and the residue treated with aqueous sodium bicarbonate, followed by methylene chloride extraction. After solvent removal the residue was recrystallized from methylcyclohexane containing a small amount of ethyl acetate to give 2.5 g (44%), mp 87-88°; ^{1}H nmr (deuteriochloroform): δ 0.88 (t, 3H, CH_2CH_3), 1.4 (m, 2H, CH_2CH_3), 2.38 (s, 3H, 2-CH_3), 3.2 (m, 1H, 4-H), 3.3 (s, 1H, OH), 3.68 and 3.74 (2s, 6H, OCH_3), 5.55 (s, 1H, =CH), 11.0 (broad, 1H, NH); ^{19}F nmr (s, CF_3); ms: glc/ci m/e 349.

Anal. Calcd. for $C_{15}H_{18}F_3NO_5$: C, 51.58; H, 5.19; N, 4.01. Found: C, 51.53; H, 5.20; N, 4.00.

Ethyl 2,7-Bis(trifluoromethyl)-1,4-dihydro-1,4-dimethyl-5-oxo-5*H*-pyrano[4,3-*b*]pyridine-3-carboxylate (**5a**).

The fractions 3-15 from Chromatotron purification described for **4a** were collected as product. After evaporation of eluting solvent, the residue was Kugelrohr distilled at 115-125° (0.15 mm Hg) followed by recrystallization from hexane to give 0.20 g (40%), mp 92-94°; ^{1}H nmr (deuteriochloroform): δ 1.2 (d, 3H, 4-CH_3), 1.22 (t, 3H, CH_2CH_3), 3.30 (q, 3H, N-CH_3 coupled to CF_3), 3.8 (m, 1H, 4-H), 4.26 (2H, CH_2CH_3), 6.6 (s, 1H, =CH); ^{19}F nmr (s and q, 2CF_3 with one coupled to CH_3); ms glc/ci m/e 385.

Anal. Calcd. for $C_{15}H_{13}F_6NO_4$: C, 46.8; H, 3.40; N, 3.64. Found: C, 47.2; H, 3.56; N, 3.48.

Ethyl 1,4-Dihydro-4-methyl-5-oxo-2,7-bis(trifluoromethyl)-5*H*-pyrano[4,3-*b*]pyridine-3-carboxylate (**5d**).

The crystals from toluene as described above in the procedure for **4d** weighed 0.2 g (9%), mp 175-176°; ^{1}H nmr (mixture deuteriochloroform and deuteriodimethyl sulfoxide) δ 1.20 (d,

3H, 4-CH_3), 1.25 (t, 3H, CH_2CH_3), 3.9 (q, 1H, 4-H), 4.3 (t, 2H, CH_2CH_3), 7.0 (s, 1H, =CH), 9.78 (broad, 1H, N-H); ^{19}F nmr (2s, $2CF_3$); ms: glc/ci m/e 371.

Anal. Calcd. for $C_{14}H_{11}F_6NO_4$: C, 45.30; H, 2.99; N, 3.77. Found: C, 45.21; H, 3.01; N, 3.72.

Dimethyl 1,4-Dihydro-1-(methoxymethyl)-4-(2-methylpropyl)-2,6-bis(trifluoromethyl)-3,5-pyridinedicarboxylate (**7a**).

Material **6** [3] (7.8 g, 20 mmoles) was added to an equivalent amount of lithium tetramethylpiperidine at 10-25° in 30 ml of dry tetrahydrofuran. After 0.5 hour, 3.5 g (28 mmoles) of bromomethyl methyl ether was added. Reaction occurred readily at room temperature with salt forming over 0.5 hour; glc indicated no **6**. The reaction mixture was poured into a mixture of ice in concentrated hydrochloric acid, followed by extraction with methylene chloride. The organic layer was then vacuum treated to remove solvent; leaving a residue of 6.5 g. Kugelrohr distillation gave 5.8 g, which upon recrystallization gave 3.5 g plus a second crop of 0.8 g (50%); mp 59-61°. From the filtrate was recovered 1.26 g of oil (see preparation for **8a** below); ^1H nmr (deuteriochloroform): δ 0.8 (d, 6H, $CH(CH_3)_2$), 1.58 (m, 1H, $CH_2CH(CH_3)_2$), 3.48 (s, 3H, OCH_3), 3.7 (m, 1H, 4-H), 3.90 (s, 6H, 2 OCH_3), 4.8 (broad s, 3H, N-CH_3 remotely coupled to CF_3); ^{19}F nmr (broad s, CF_3 remotely coupled to N-CH_3); ms: glc/ci m/e 433.

Anal. Calcd. for $C_{17}H_{21}F_6NO_5$: C, 47.12; H, 4.88; N, 3.23. Found: C, 47.24; H, 4.99; N, 3.22.

Dimethyl 1,4-Dihydro-1-methyl-4-(2-methylpropyl)-2,6-bis(trifluoromethyl)-3,5-pyridinedicarboxylate (**7b**).

Material **6** (7.8 g, 20 mmoles) was reacted in dry tetrahydrofuran with 0.02 mole of lithium diisopropylamide at -78°. Excess methyl iodide was then added at this temperature, and the contents allowed to warm to room temperature, whereupon salt formation was evident. Workup similar to that described for **7a** gave 7.4 g (95%) of oil upon Kugelrohr distillation. This material proved identical with **6**. The above reaction was repeated except the litho base was derived from 2,2,6,6-tetramethylpiperidine. With occasional monitoring by glc the mixure was eventually heated to 40° for 48 hours, adding several grams of additional methyl iodide from time-to-time. Upon cooling the reaction mixture was contacted with ice and hydrochloric acid with extraction by methylene chloride. After vacuum removal of solvent the residue weighed 8.4 g, which after Kugelrohr distillation, bp 130-160° (0.5 mm Hg) gave 1.0 g of residue and 6.9 g of distillate; the latter by glc analysis contained 90% of **7b** and 10% of **6**. Hplc of 6 g with 1% ethyl acetate in cyclohexane gave product fractions 4 and 5, containing 1.9 g (27%) of soft crystals, mp 30°; ^1H nmr (deuteriochloroform): δ 1.8 (d, 6H, $CH(CH_3)_2$), 1.40 (m, 2H, CH_2), 1.7 (m, 1H, $CH(CH_3)_2$), 3.20 (q, 3H, N-CH_3 remotely coupled to CF_3), 3.7 (m, 1H, 4-H), 3.80 (s, 6H, OCH_3); ^{19}F nmr (broad s, CF_3 remotely coupled to NCH_3); ms: glc/ci m/e 403.

Anal. Calcd. for $C_{16}H_{19}F_6NO_4$: C, 47.65; H, 4.75; N, 3.47. Found: C, 47.68; H, 4.77; N, 3.47.

Dimethyl 3,4-Dihydro-3-(methoxymethyl)-4-(2-methylpropyl)-2,6-bis(trifluoromethyl)-3,5-pyridinedicarboxylate (**8a**).

The oily filtrate derived from the preparation of **7a** was subjected to Chromatotron separation with 1.2% ethyl acetate in cyclohexane to give pure compound in fractions 5-7, which after Kugelrohr distillation at 160° (1.5 mm Hg) weighed 0.3 g; n_D^{27} 1.4290; ^1H nmr (deuteriochloroform): δ 0.81 and 0.83 (2d, 6H, $CH(CH_3)_2$), 1.35 (m, 2H, CH_2CH), 3.12 (m, 1H, 4-H), 3.2 (s, 3H, CH_2OCH_3), 3.77 (AB quartet, 2H, CH_2OCH_3), 3.77 and 3.83 (2s, 6H, OCH_3). Irradiation of 4-H at δ 3.12 simplified absorption of the δ 1.35 multiplet to unsymmetrical doublets while irradiation of CH_2CH at δ 1.35 much reduced multiplicity of the δ 3.12 absorption; no other regions were affected by these experiments. ^{19}F nmr (s, CF_3), (d, J = 2 Hz, CF_3); ms: glc/ci m/e 433.

Anal. Calcd. for $C_{17}H_{21}F_6NO_5$: C, 47.12; H, 4.88; N, 3.23. Found: C, 47.34; H, 5.01; N, 3.22.

Dimethyl 1,2-Dihydro-1-(methoxymethyl)-4-(2-methylpropyl)-2,6-bis(trifluoromethyl)-3,5-pyridinedicarboxylate (**9**).

Material **7a** (0.8 g, 1.8 mmoles) and 0.3 g of DBU were heated to reflux in 20 ml of tetrahydrofuran. After 1 hour, glc indicated a new (longer) retention peak, with no trace of **7a**. The reaction mixture was washed next day with dilute hydrochloric acid and water, with extraction by methylene chloride. After Kugelrohr distillation, Chromatotron separation with 1% ethyl acetate in cyclohexane gave 0.3 g (38%) of oil, n_D^{27} 1.4455; ^1H nmr (deuteriochloroform): δ 0.78, 0.9 (2d, 6H, $CH(CH_3)_2$), 1.5-3.25 (multiplets, 3H, CH_2-CH), 3.39 (s, 3H, OCH_3), 3.90 (s, 6H, 2 OCH_3), 4.65 (AB q, 2H, N-CH_2), 5.40 (q, 1H, 2-H coupled to 2-CF_3); ^{19}F nmr (s, CF_3), (d, J = 6 Hz, CF_3 coupled to 2-H); ms: glc/ci m/e 433.

Anal. Calcd. for $C_{17}H_{21}F_6NO_5$: C, 47.12; H, 4.88; N, 3.23. Found: C, 47.15; H, 4.88; N, 3.20.

Methyl 2-(Difluoromethyl)-1,2-dihydro-4-(2-methylpropyl)-5-(1*H*-pyrazol-1-ylcarbonyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (**11c**).

To a solution of 15.1 g (0.037 mole) of **10c** in 125 ml of dimethylformamide was added 1.4 g (0.037 mole) of sodium borohydride in portions. The mixture was heated to 50°, and maintained at this temperature for 2 hours. An additional 1.0 g (0.026 mole) of sodium borohydride was added and the reaction continued for 1 hour longer at 50°. After cooling, the reaction mixture was slowly added to a stirred solution of dilute hydrochloric acid, with methylene chloride rinses. The combined methylene chloride extracts gave 24.5 g of oil after solvent removal. Purification of 6.8 g of this oil by hplc using 2.5% ethyl acetate in cyclohexane, followed by Kugelrohr distillation afforded 1.28 g (30%) of greenish yellow viscous oil, bp 145-155° (0.12 mm Hg); ^1H nmr (deuteriochloroform): δ 0.65 and 0.83 (2d, 6H, $CH(CH_3)_2$), 3.7 (s, 3H, OCH_3), 6.4, 7.65, 8.2 multiplets, 3H, pyrazol 3,4,5-H), other multiplets for remaining protons between 1.2-3.2 and 4.2-7.2 ppm; ^{19}F nmr δ -66.31 (s, CF_3), -127 to -132 (m's, CF_2H).

Anal. Calcd. for $C_{17}H_{18}F_5N_3O_3$: C, 50.13; H, 4.45; N, 10.32. Found: C, 50.14; H, 4.45; N, 10.25.

Dimethyl 2-(Difluoromethyl)-1,2-dihydro-1-(methoxymethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**13a**), Mixture with Dimethyl 6-(Difluoromethyl)-1,2-dihydro-1-(methoxymethyl)-4-(2-methylpropyl)-2-(trifluoromethyl)-3,5-pyridinedicarboxylate (**14a**).

Material **10a** [3] (5 g, 13.5 mmoles) was reacted in dimethylformamide at 50-60° with 0.51 g of sodium borohydride for 2 hours. After this time a 1.1 x molar equivalent of bromomethyl methyl ether was added, which caused an exotherm, with the temperature momentarily exceeding 55°. There was a transient precipitation of salt. After cooling to 30° the reaction mixture was stirred a further 1.5 hours, then treated with dilute

hydrochloric acid, ice and ether. The ether layer was washed twice again with 1% hydrochloric acid, then dried over magnesium sulfate. The ether solution was filtered from drying agent, then evaporated of solvent to give 5.5 g of residue. Kugelrohr distillation at 120-175° (2 mm) gave 5.0 g of distillate consisting of nearly a 50:50 mix of *N*-methyl and *N*-hydrogen compounds, each divided between 1,2 and 1.6-dihydro-isomers. The distillate was subjected to hplc with 2% ethyl acetate in cyclohexane to give fractions 7-13 as *N*-alkylated product, weight 2.5 g (45%) with material **13a** 75% of product and **14a** as 25% of product as determined by ^{19}F nmr, and glc/ms; n_D^{27} 1.4605; ^{19}F nmr (deuteriochloroform) (s, 0.75 x 3F, CF_3), (d, 0.25 x 3 F, CF_3 coupled to vicinal H), (4d, 0.75 x 2F, prochiral, vicinal and geminal coupling to 2-H and CHF_2 respectively), (2d, 0.25 x 2F, prochiral and geminal coupling to CF_2); ms: glc/ci m/e 415 (75%), m/e 415 (25%).

Anal. Calcd. for $C_{17}H_{22}F_5NO_5$: C, 49.16; H, 5.34; N, 3.37. Found: C, 49.29; H, 5.39; N, 3.36.

S,S-Dimethyl 2-(Difluoromethyl)-1,2-dihydro-1-(methoxymethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarbothioate (**13b**), Mixture with *S,S*-Dimethyl 6-(Difluoromethyl)-1,2-dihydro-1-(methoxymethyl)-4-(2-methylpropyl)-2-(trifluoromethyl)-3,5-pyridinedicarbothioate (**14b**).

Material **10b** (4 g, 10 mmoles) was mixed in dimethylformamide with 0.62 g of sodium borohydride and heated at 50-60° for 2 hours, then cooled to 25°. Bromomethyl methyl ether (2 g, 16 mmoles) was added with stirring. The reaction was monitored by glc and ^{19}F nmr. Treatment after 2 hours with dilute hydrochloric acid and ether extraction, then evaporation, gave a residue that was Kugelrohr distilled. Hplc with 1% ethyl acetate in cyclohexane gave the product in fractions 4-7, followed by a second distillation of these fractions gave 0.9 g (20%) of yellow oil, n_D^{25} 1.5151, having 58% **13b** and 42% **14b** content, as determined by ^{19}F nmr inspection of CF_3 absorptions; ^{19}F nmr (deuteriochloroform): (s, 0.58 x 3F, CF_3), (d, 0.42 x 3F, CF_3 coupled to vicinal H); ms: glc/ci m/e 447, (60%) 447 (40%).

Anal. Calcd. for $C_{17}H_{22}F_5NO_3S_2$: C, 45.63; H, 4.96; N, 3.13; S, 14.33. Found: C, 45.39; H, 5.12; N, 3.11; S, 14.34.

Methyl 2-(Difluoromethyl)-1,2-dihydro-1-methyl-4-(2-methylpropyl)-5-(1*H*-pyrazol-1-ylcarbonyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (**13c**).

Material **11c** (2.1 g, 5.2 mmoles) was dissolved in tetrahydrofuran and 6 ml of 1 *N* lithium bis(trimethylsilyl)amide was added at -30°. Excess methyl iodide was then added, warmed to room temperature, then to 35°. After several hours between 25-35° the contents were contacted with ice, dilute hydrochloric acid and methylene chloride. The organic layer was separated and vacuum treated to give 2.6 g residue. Dividing the residue in half, two separate Chromatotron separations with 5-10% ethyl acetate in cyclohexane were carried out. All eluted material was product, which upon solvent evaporation gave 1.4 g; Kugelrohr distillation gave 1.0 g of yellow oil (46%) which by ^{19}F and ^1H nmr was shown to be only a single isomer, n_D^{25} 1.4997; ^1H nmr (deuteriochloroform): δ 0.72 and 0.88 (2s, 6H, prochiral $CH(CH_3)_2$), 1.68 (m, 1H, $CH(CH_3)_2$), 2.45 and 3.0 (2 m's, 2H, prochiral CH_2), 3.28 (s, 3H, NCH_3), 3.8 (s, 3H, OCH_3), 4.8 (m, 1H, 2-H), 6.34 (set of 3 m's, 1H, CHF_2), 6.48, 7.62, 8.28 (3 m's, 3H, 3,4,5-pyrazole-H); ^{19}F nmr, (broad s, CF_3), (4d, 2F, prochiral CHF_2 with geminal and vicinal coupling to H).

Anal. Calcd. for $C_{18}H_{20}F_5N_3O_3$: C, 51.31; H, 4.78; N, 9.97. Found: C, 51.55; H, 4.82; N, 9.75.

Dimethyl 2-(Difluoromethyl)-1,2-dihydro-1-methyl-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**13d**), Mixture with Dimethyl 6-(Difluoromethyl)-1,2-dihydro-1-methyl-4-(2-methylpropyl)-2-(trifluoromethyl)-3,5-pyridinedicarboxylate (**14d**).

A mixture of 1,2 and 1,6-dihydropyridines **11a** and **12a**, 7.4 g (20 mmoles), prepared by sodium borohydride reduction of **10a**, see above and reference [3], was dissolved in 30 ml of tetrahydrofuran and at -30° 24 mmoles lithium bis(trimethylsilyl)amide (24 ml of 1 *N* solution) added. After 15 minutes excess methyl iodide was introduced at this temperature then the mixture allowed to warm to room temperature. Using a warm water bath the reaction mixture was then heated to 35° and more alkylating agent added. Although the retention time for starting materials and products were nearly identical, glc/ms revealed complete reaction. Treatment next day with ice and dilute hydrochloric acid and methylene chloride extraction gave, upon solvent evaporation 6.7 g residue. Kugelrohr distillation at 120-160° (2 mm Hg) afforded 5.95 g (77%) with 0.6 g residue. The oily distillate was shown by ^{19}F nmr to be 49% **13d** and 51% **14d**; ^1H nmr (deuteriochloroform): δ 0.75-0.95 (4d, 6H, prochiral $CH(CH_3)_2$), 1.6 and 1.8 (2 m's, 1H, $CH(CH_3)_2$, 2.51 and 2.91 (2 sets m's, 2H, prochiral CH_2CH), 3.2 3.38 (2s, 3H, NCH_3), 4.76-4.79 (4s, 6H, OCH_3), 4.71 (m, 0.49H, 2-H), 5.1 (q, 0.51H, 2-H), 5.6 (4 sets of doublets, 0.49H, CHF_2), 6.87 (t, 0.51H, CHF_2); ^{19}F nmr (s, 0.49 x 3F, CF_3), (d, 0.51 x 3F, CF_3), (many m's due to isomeric mixture, prochirality and ^1H coupling, 2F, CHF_2).

Anal. Calcd. for $C_{16}H_{20}F_5NO_4$: C, 49.87; H, 5.23; N, 3.63. Found: C, 49.82; H, 5.23; N, 3.62.

Dimethyl 1-(Chloroacetyl)-2-(difluoromethyl)-1,2-dihydro-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**13e**).

A 50:50 mixture of **11a** and **12a**, (3.7 g, 10 mmoles) was dissolved in 30 ml of tetrahydrofuran, cooled to -30° and 14 ml of a 1 *N* solution of lithium bis(trimethylsilyl)amide added. After stirring 0.5 hour, 1.5 ml of chloroacetyl chloride was introduced at that temperature, then the mixture permitted to warm to room temperature. Glc and ms confirmed the presence of both starting material and higher boiling product. The reaction mixture was recooled to -30°, more lithio base and chloroacetyl chloride added, and once again the mixture allowed to warm slowly to room temperature, with a brief (5 minutes) heating period at 50°; these operations failed to give additional product or derivation of starting material. The reaction mixture was then treated with dilute hydrochloric acid with extraction by methylene chloride. Kugelrohr distillation of the organic residue gave 0.9 g of nonvolatiles and 5.0 g of distillate at 140-180° (1.5-2 mm Hg). The distillate was then subjected to hplc with 35% methylene chloride in cyclohexane to give pure product in fractions 6 and 7, total 0.75 g (17%), n_D^{24} 1.4750. It was determined that the compound possessed an amide rather than ketonic carbonyl by ir, 1735 cm^{-1} (ester CO), 1710 cm^{-1} (amide CO); highfield ^{13}C, ^1H and ^{19}F nmr defined the structure as 1,2-dihydro isomer with only a trace at most of 1,6 isomer; ^1H nmr (deuteriochloroform): δ 0.78, 0.88 (2d, 6H, prochiral $CH(CH_3)_2$), 1.7 (m, 1H, $CH(CH_3)_2$), 2.0, 3.3 (2 sets of 2d's, 2H, prochiral CH_2CH), 3.85, 3.90 (2s, 6H, OCH_3), 4.25 (AB q, 2H, prochiral $ClCH_2$), 5.5 (m, 1H, 2-H), 5.8 (t

(each split again into d's), 1H, CHF_2); ^{19}F nmr (s, CF_3), (4 d's prochiral CHF_2); ^{13}C (^1H decoupled) nmr δ 53.05 (t, *C*HCHF$_2$); ms: glc/ci m/e 477 (1 Cl).

Anal. Calcd. for $C_{17}H_{19}ClF_5NO_5$: C, 45.60; H, 4.28; Cl, 7.92; N, 3.13. Found: C, 45.94; H, 4.38; Cl, 7.60; N, 3.01.

Dimethyl 2-(Difluoromethyl)-1,2-dihydro-4-(2-methylpropyl)-1-[(trichloromethyl)thio]-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**13f**).

A mixture of 1,2 and 1,6 dihydro compound **11a**, **12a** (from sodium borohydride reduction of **10a**) (3.7 g, 10 mmoles) was dissolved in 20 ml of tetrahydrofuran contained in a 100 ml, 3 neck flask fitted with nitrogen flush and provided with magnetic stirring. At -30°, 14 ml of 1 *N* (excess) lithium bis(trimethylsilyl)-amide was added, and the mixture stirred for 30 minutes at -30°; the mixture turning dark amber at this stage. Perchloromethyl mercaptan, 2 g (10 mmoles) was then added *via* syringe. There was an instant color lightening. The mixture was then allowed to warm to room temperature by withdrawal of the cooling bath. Tlc showed complete reaction of starting material with formation of two separate and distinct compounds. Consequently the reaction mixture was treated with dilute hydrochloric acid and extracted with methylene chloride, then vacuum treated under final oil pump vacuum at 85-90° to remove vestiges of perchloromethyl mercaptan. The 5.2 g residue was a reddish brown viscous but mobile oil. Elution through a hplc column with 1.2% ethyl acetate in cyclohexane gave **13f** in fractions 5-7. These fractions, after solvent removal was Kugelrohr distilled at 160-180° (1.5-2 mm Hg) to give 1.44 g (28%), n_D^{26} 1.4933; ^1H nmr (deuteriochloroform): δ 0.88, 0.94 (2d, 6H, prochiral CH(C*H*$_3$)$_2$), 1.76 (m, 1H, C*H*(CH$_3$)$_2$), 2.0, 3.32 (2 sets of 2d's, 2H, prochiral C*H*$_2$CH), 3.80, 3.87 (2s, 6H, OCH$_3$), 5.3 (m, 1H, 2-H), 5.7 (t of d's, 1H, CHF_2); ^{13}F nmr (s, CF_3), (4d, prochiral CHF_2); ^{13}C (^1H decoupled) nmr δ 67.26 (t, *C*-CHF$_2$), 100.37 (s, Cl$_3$*C*S), 164.5, 164.8 (2s, 2 *C*O$_2$CH$_3$); ms: Calcd. for 518.98640. Found: 518.98808 (3Cl).

Anal. Calcd. for $C_{16}H_{17}Cl_3F_5NO_4S$: Cl, 20.4; N, 2.69; S, 6.16. Found: Cl, 20.8; N, 2.75; S, 6.26.

Dimethyl 6-(Difluoromethyl)-1,2-dihydro-4-(2-methylpropyl)-1-[(trichloromethyl)thio]-2-(trifluoromethyl)-3,5-pyridinedicarboxylate (**14f**).

From the hplc described for the preparation of **13f** fractions 2, 3 were collected, solvent evaporated, the residue Kugelrohr distilled to give 1.56 g (30%), n_D^{26} 1.4974; ^1H nmr (deuteriochloroform): δ 0.85, 0.90 (2d, 6H, prochiral CH(C*H*$_3$)$_2$), 1.72 (m, 1H, C*H*(CH$_3$)$_2$), 2.2, 3.32 (2 sets of 2d's, 2H, prochiral C*H*$_2$CH), 3.82, 3.85 (2s, 6H, OCH$_3$), 5.70 (q, 1H, 2-H), 6.63 (t, 1H, CHF_2); ^{19}F nmr (d, CF_3, (2d, prochiral CHF_2); ms: Calcd. for 518.98640. Found: C, 518.98759 (3Cl).

Anal. Calcd. for $C_{16}H_{17}Cl_3F_5NO_4S$: Cl, 20.4; N, 2.69; S, 6.16. Found: Cl, 20.8; N, 2.73; S, 6.24.

Dimethyl 2,6-Bis(trifluoromethyl)-3-chloro-3,4-dihydro-4-(2-methylpropyl)-3,5-pyridinedicarboxylate (**15**).

Dihydropyridine **6** [3] (4.5 g, 11.6 mmoles) was dissolved in 30 ml of tetrahydrofuran, and 13 ml of 1 *N* lithium bis(trimethylsilyl)amide added at -30°. After stirring 0.5 hour, 2.5 g (13 mmoles) perchloromethyl mercaptan was added at that temperature. There was an instant decoloration at this low temperature from light red to orange. As the temperature was raised to ambient, an exotherm was noted at 22°, with the temperature rising to 35-40° with copious precipitation of salt. After cooling to room temperature, dilute hydrochloric acid work up with methylene chloride extraction gave after solvent removal and Kugelrohr distillation, a solid identified as **16** [3], demonstrating that the above operation overall caused oxidation of the dihydropyridine **6**. The next experiment was identical with the above, except at 21°, just prior to exotherm, the material was cooled to 10-15°, stirred 15 minutes, then worked up in identical fashion to the above. In this operation no dehydrochlorination took place, even upon Kugelrohr distillation. Rather, larger hexagonal crystals formed from the distillate over two days. The solid material was separated from the mother liquor, recrystallized from cold methanol to afford 2.5 g (51%) crystals, mp 45-46°; ^1H nmr (deuteriochloroform): δ 0.82 and 0.85 (2d, 6H, prochiral CH(C*H*$_3$)$_2$), 1.25, 1.36, 1.47 (3 sets of m's, 3H, C*H*$_2$C*H*(CH$_3$)$_2$), 3.31 (t, 1H, 4-H), 3.89 (broad s, 6H, OCH$_3$); ^{19}F nmr (2s, CF_3). X-ray crystal structure for **15** $C_{15}H_{16}ClF_6NO_4$, monoclinic, space group $C_{2/c}$-C^6_{2h} (No. 15), with a = 9.788 (1)A, b = 18.517(3)A c 20.156(4)A; B = 91.76(1)°, V = 3651.4(4)A^3; Z = 8, ν = 2.815 and D (Calcd) = 1.498 g/cm^3. Intensity data were collected in the standard Θ/2Θ scan mode at -130° using graphite monochromated $Mo_{k\alpha}$ radiation. Final convergence was reached at R_1 = 0.041 and R_w = 0.051 for 1896 reflections, with an error in an observation of unit-weight of 1.847.

Anal. Calcd. for $C_{15}H_{16}ClF_6NO_4$: C, 42.52; H, 3.81; Cl, 8.37; N, 3.31. Found: C, 42.52; H, 3.82; Cl, 8.39; N, 3.28.

Acknowledgement.

The author gratefully acknowledges Dr. L. F. Lee for providing, *via* his original Hantzsch sequences and borohydride chemistry, certain of the dihydropyridines and pyridines used as starting materials for this study. He is also indebted to J. M. Molyneaux for preparing certain other dihydropyridines as starting materials. Drs. M. Thompson and J. Olgivie are responsible for the X-ray crystallography results reported here.

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[4] In spite of formal nomenclature rules, but for the sake of consistency where applicable, the 2 and 6-positions of the pyridines in the Discussion are arbitrarily assigned to those nuclear carbons attached respectively to the difluoromethyl and trifluoromethyl groups. Correct nomenclature is given in the Experimental.

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