Synthesis of 2/6-(Polychloromethyl)pyridinecarboxylates

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Due to their relationship to certain bio-active 2,6-(polyfluoromethyl)-3,5-pyridinedicarboxylates **12**, methodology was developed to prepare new, but analogous 2/6 (polychloromethyl)pyridinecarboxylates **6, 9, 10, 13, 18** and **20**. Successful methods to prepare these materials include several chlorination procedures, mixed Hantzsch sequences, and aluminum chloride interchanges with **12** and **16**.

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Recent modifications of the Hantzsch synthesis have made available, from trifluoroacetoacetates, the novel 4-alkyl-3,5-pyridinedicarboxylates substituted with polyfluoromethyl in the 2 and/or 6 positions [1]. The herbicidal activity of these materials [1] caused us to undertake studies, herein described, to prepare a number of related but heretofore unknown 2/6-polychloromethyl-3,5-pyridinedicarboxylates.

The most obvious route to polychloromethylpyridines is the direct chlorination with molecular chlorine and this method has been reported for simple methylpyridines (*e.g.* 2,6-lutidine [2]). However, the chlorination of 2,6-dimethyl-3,5-pyridinedicarboxylates, typical end products of the Hantzsch pyridine synthesis, has not been reported. In the case of 4-alkyl-3,5-pyridinedicarboxylates, chlorination could occur on the 4-alkyl group or even on the *O*-alkyl group of the ester function as well as the 2,6-methyl groups. The relatively easy condensation of aldehydes with the 2- or 6-alkyl groups [3] indicated that methylene carbanions could be formed which would readily chlorinate, especially after the introduction of the first chlorine atom. This could, of course, also occur at the 4-alkyl group. For this reason chlorinations of 2,6-dimethyl-3,5-pyridinedicarboxylates were attempted using basic catalysts. Another reason for the inclusion of bases was to neutralize the hydrogen chloride formed which would protonate the pyridines and render them unreactive.

Attempts to chlorinate the pyridine **8a** in various solvents with a variety of catalysts and bases and at 10-110° led to random chlorination which involved the isobutyl group as well as the 2,6-methyl groups. Similar attempts to chlorinate **8b** gave chlorination of the *O*-methyl groups as well as the 2,6-methyl groups.

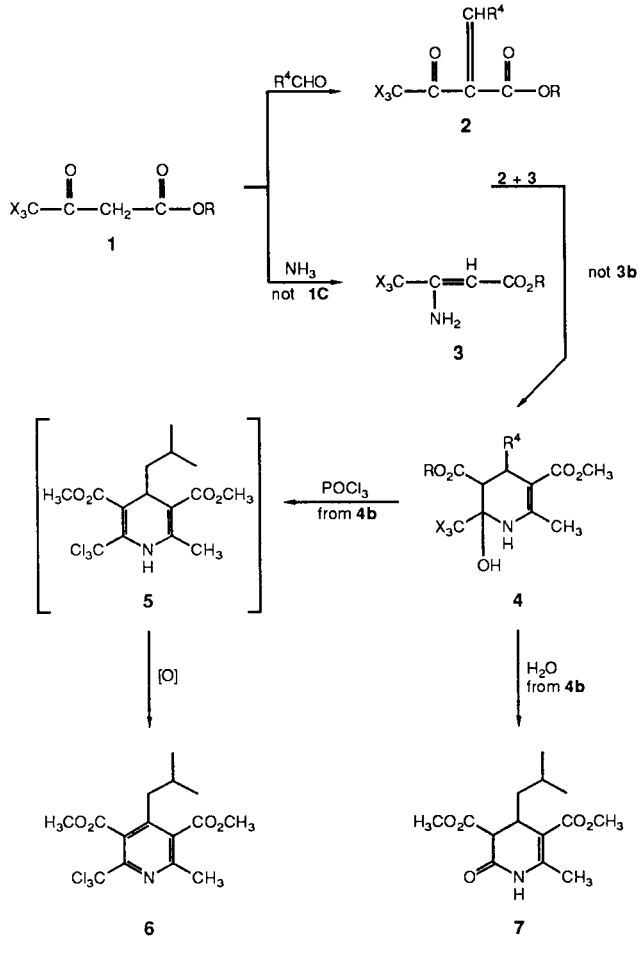
Another obvious route to the polychloromethylpyridines would be the use of the Hantzsch pyridine synthesis. The classical Hantzsch synthesis [4] of the bis-trichloromethyl derivatives would involve the reaction of two moles of methyl-4,4,4-trichloroacetoacetate, **3c**, with the appropriate aldehyde and ammonia. However, **3c** has been reported to give methyl malonamate and chloroform on treatment with ammonia [5]. This indicated that the conventional Hantzsch synthesis would be difficult or impossible in this case. Attempted synthesis with **3c** by reaction with isovaleraldehyde or paraformaldehyde and ammonia with 2,6-lutidine or triethylamine in methanol gave dimethyl malonate as the major product. It was found that **3c** in ethanol with triethylamine rapidly gave methyl ethyl malonate and chloroform. In aprotic solvents with ammonia methyl malonamate was produced.

A favored mechanism of the Hantzsch synthesis is the formation of an alkylidene derivative **2** and an enamine **3** which react to form dihydropyridine [6]. If two different acetoacetic esters are used, mixtures are formed. It is possible that by preforming the alkylidene derivative and/or the enamine, mixed Hantzsch reactions could be carried out without scrambling. This hypothesis was tested by reacting paraformaldehyde and ethyl-4,4,4-trifluoroacetoacetate, **1b** with methyl 2-aminocrotonate **3a**. The resulting hydrate **4a** was formed in good yield without apparent scrambling. However, when this type of reaction was attempted with **1c** in ethanol, the major products were methyl ethyl malonate and **8b**. The latter must have been formed by reaction of two moles of **3a** with formaldehyde, a result which is a known modification of the Hantzsch reaction [7]. Apparently reaction of formaldehyde with **1c** is too slow to compete with this reaction. When the alkylidene **2a** was prepared and isolated (*cis* and *trans* forms) by aldol condensation and distillation, reaction of it with **3a** gave the hydrate **4b** in 40% yield when recrystallized from methanol. Attempts to recover a second crop of **4b** gave the pyridone **7** but this was found to be an artifact of the workup and was present in only trace quantities in the reaction mixture. Since eight isomers are possible for **4b**, it was surmised that the other products from the reaction were merely isomers of the product which crystallized. With this in mind, the whole reaction mass was subjected to dehydration conditions by treatment with phosphorus oxychloride which led to the formation of unstable intermediates, one of which is tentatively identified by spectral evidence and subsequent reaction as being a dihydropyridine **5**, which in turn were oxidized to the pyridine **6**.

The reverse sequence, reaction of methyl 4,4,4-trichloro-

3-aminocrotonate **3b**, (which can be prepared from trichloroacetonitrile and methyl acetoacetate [8]), with isovaleraldehyde and methyl acetoacetate, was not successful. Apparently the trichloroenamine is not nucleophilic enough to undergo the mixed Hantzsch reaction. (Scheme 1).

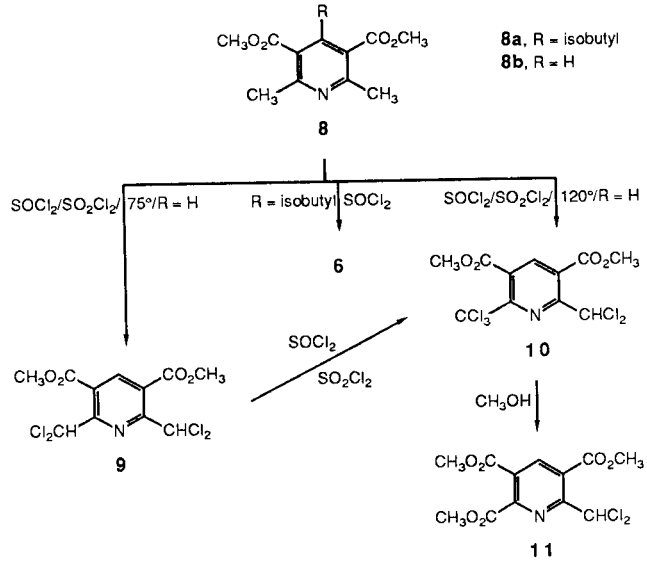
Scheme 1



1a, X = H, R = CH_3
1b, X = F, R = C_2H_5
1c, X = Cl, R = CH_3
2a, X = Cl, R = CH_3, R^4 = isobutyl
3a, X = H, R = CH_3
3b, X = Cl, R = CH_3
4a, X = F, R = C_2H_5, R^4 = H
4b, X = Cl, R = CH_3, R^4 = isobutyl

With the obvious limitations of these routes, our attention returned to chlorination. Reaction of thionyl chloride with methylpyridines has been reported [9] to produce trichloromethyl derivatives. Initial moderate temperature reactions of thionyl chloride with **8a** gave mixtures, but in an autoclave at 120°, **6** was produced. This reaction was surprisingly clean with no tar formation. An attempt to prepare the bis-trichloromethyl derivative, however, by reaction at 180° produced tar and sulfur (S_8, mass 256). The probable source of the sulfur is formation and reaction of sulfur dichloride. Since an oxidation must take place to convert (S = O) to sulfur dioxide, thionyl chloride is reduced. The sulfur produced is incompatible with the trichloromethyl pyridine and decomposition results. A reaction run with sulfur dichloride did produce sulfur. If an oxidizing agent were to be included in the reaction this could be avoided and the ideal agent would be sulfuryl chloride which would simply lead to thionyl chloride. Thus, in theory, the reaction could be run with sulfuryl chloride and a catalytic amount of thionyl chloride. Reaction of **8a** with these led to a mixture; however, reaction with **8b** gave the 2,6-bis(dichloromethyl) derivative **9**. The formation of **9** rather than the trichloromethyl derivative was unexpected but the proton nuclear magnetic resonance spectrum was unequivocal. Perhaps steric hindrance to the introduction of the third chlorine atom is an explanation for this unexpected result. Reaction of **8b** at 120° gave cleanly the pentachloro derivative **10**. The pentachloro derivative **10** could also be prepared from **9** but the reaction was slower than with **8b** and in one case, where methanol was added in order to reesterify any acid chloride which may have been formed, the triester **11** was isolated. (Scheme 2).

Scheme 2



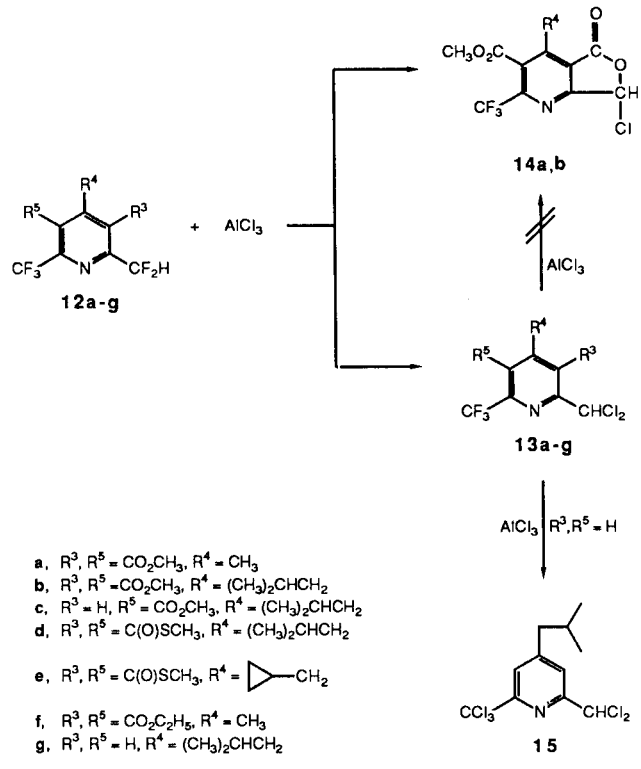
Numerous attempts were made to exchange chlorine for fluorine in **6**, **9** and **10** using potassium fluoride in various solvents or anhydrous hydrogen fluoride with and without antimony trifluoride/antimony pentachloride catalysis at temperatures up to 160°. This resulted in recovery of starting material or tar depending on conditions and in no case were C-F absorptions observed in the fluorine nuclear magnetic resonance spectra of the reaction mixtures.

Although use of the mixed Hantzsch and chlorination of 2,6-dimethylpyridinedicarboxylates, as enumerated above, proved partially successful for preparing the title com-

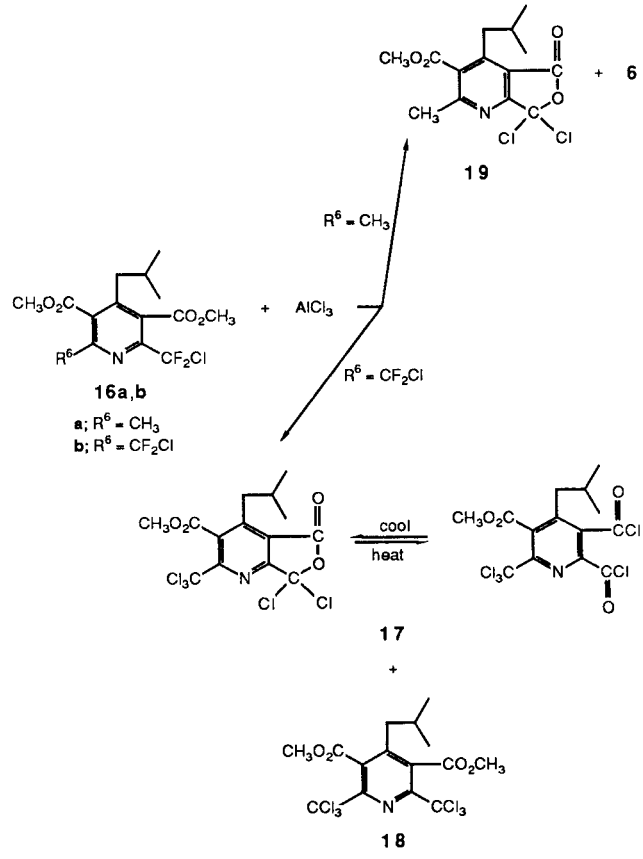
pounds, these methods would clearly have to be supplemented to complete studies mentioned in the introductory paragraph. One such method utilizes as reactants, the cited 2,6-fluoroalkyl-containing pyridines available *via* Hantzsch and sequential reactions [1] with metal chlorides to give the desired polychloromethylpyridinecarboxylates. Metal chloride/fluoroalkyl exchange to produce C-Cl bonds has rarely been used, since usually the more desired reaction is the reverse, namely C-F bond formation from C-Cl with metal or hydrogen fluorides. Nevertheless a few examples do exist in the literature wherein high temperature or Friedel Crafts interchange of aluminum chloride with relatively simple C-CF_3 compounds or interchanges involving rearrangements in aliphatic fluoroalkyl-compounds (usually freons) have formed polychloromethyl moieties [10a-c]. Studies with the functionalized pyridines under study here then, would represent a useful and illuminating extension of this little-used conversion.

Scheme **3** shows the reaction of aluminum chloride with pyridines **12**, [1]. The reaction can conveniently be carried out in nitromethane (CAUTION, see ref [15]) or methylene chloride solvents at ambient temperatures, up to reflux. Generally an exotherm is observed, and with larger quantities of reactant, ice bath cooling and/or portionwise addition of aluminum chloride is necessary. Generally the reaction is complete only upon addition of excess metal chloride (equal weights of pyridine substrate and aluminum chloride where found expedient). Providing the pyridine substrate possessed at least one 3 or 5 carboxylate modification, only the -CHF_2, but not the CF_3 substituent is converted, forming **13**, even in boiling nitromethane. Moreover, if the 2-CHF_2 group is flanked by a 3-carboxylic ester function, chlorolactone, **14** formation can also take place. Chlorolactone presumably arises from interaction of the more reactive 2-CHF_2 or 2-CHFCl intermediate (the latter detected during the reaction only in trace amounts) with adjacent ester, since purified **13**, possessing the 2-$CHCl_2$ moiety could not be converted to lactone **14** with fresh aluminum chloride, even in refluxing nitromethane [11]. Chlorolactone formation could be minimized or eliminated by moderating temperature and employing less reactive carboxyl moieties such as *O*-ethyl or *S*-methyl esters. Finally, the only case encountered wherein the fluoroalkyl-containing pyridine demonstrated interchange with trifluoromethyl was with 3,5-unsubstituted pyridine, **12g**. In this instance both the dichloro and pentachloropyridines (**13g** and **15**) were isolated from this exothermic reaction. It would be useful to examine other trifluoromethyl containing heterocycles for their ease of chlorine fluorine interchange. Apparently the absence of both carboxyl groups enhances this reaction, perhaps by increasing the complexing of the pyridine nitrogen with aluminum chloride.

Scheme 3



Scheme 4



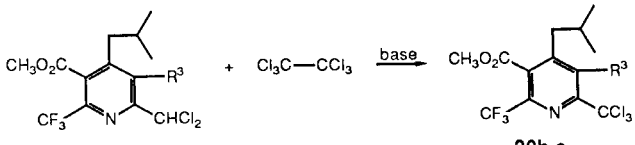
The reaction of metal chlorides was extended to include $-CF_2X$ groups wherein X = Cl, CH_3, and Me_3Si. These latter groups resembled hydrogen rather than fluorine in their labilizing effect, thus easily affording fluorine/chlorine interchange [12]. Scheme **4** gives the results when X = Cl.

The inertness of CF_3 *vs* CF_2X can best be rationalized by assuming the fluorine atoms in trifluoromethyl reinforce the tightly held carbon-fluorine bond, making it difficult for even a strong Lewis acid such as aluminum chloride to complex and extract the crucial first fluorine atom. Apparently having two rather than three geminal fluorine atoms sufficiently changes the remaining fluorine lability so that either smaller (*i.e.* H), or larger (CH_3, Cl, Me_3Si) groups, electron donating (CH_3, Me_3Si), or an electron attracting group (Cl) permit the interchange.

It can be noted from Scheme **4** that the CF_2Cl group is readily converted to $-CCl_3$. However lactone is also formed as evidenced by **17** and **19**. The former material was a very crystalline white solid, easily recrystallized without change from cold methanol. Nevertheless the melting point is surprisingly very broad (118 - >140°) despite sharp, clean nmr absorptions and a single glc peak. This behavior suggests **17** is a ring-chain tautomer as is found for phthaloyl chloride [13]. Support for this situation was gained by comparing room temperature and glc/ft ir (see Experimental).

Materials **13** obtained from aluminum chloride treatment could in turn easily be transformed to pyridines **20**, containing the trichloromethyl moiety. Methodology as shown in Scheme 5 is similar to recent chemistry developed for the preparation of certain substituted benzotrichlorides from benzyl and benzal chlorides [14]. Note that the greater acidity of the affected carbon-hydrogen bond in **13**, compared with **8**, enabled the desired selective chlorination of the former to take place.

Scheme 5



13b,c **20b,c**

EXPERIMENTAL

All melting points were determined on a Laboratory Devices Mel-Temp apparatus and are uncorrected. The ^1H and ^{19}F nmr spectra were recorded on either a Varian EM-360L or EM-390 instrument referenced to tetramethylsilane and fluorotrichloromethane respectively. Exact ^{19}F chemical shifts for CF_3 were not always recorded; rather emphasis was given to number and type of multiplicity to confirm sample identity and purity. The ^{13}C nmr spectra were obtained on a Bruker WM-360 and are referenced to tetramethylsilane. Mass spectra were measured by a Varian CH-7 mass spectrometer with isobutane chemical ionization (ci) expressed as molecular weight (*i.e.*, m/e). Where applicable, the number of chlorine atoms per molecule is expressed as determined by the ms isotope ratio. Liquid chromatography (hplc) was done with a one foot Whatman Partisil 5 ccs/C_8 25 column with 75% acetonitrile as a mobile phase and uv detector, or a Waters Prep LC, model 500A, with refractive index detector. Microanalyses were performed by Atlantic Microlab Inc., Atlanta, Georgia 30366.

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

To methyl acetoacetate (232.2 g, 1.0 mole) containing diethylamine (25 drops) was added 86.1 g (1.0 mole) of isovaleraldehyde over 1 hour with cooling. Methanol was added (50 g) and 17 g of anhydrous ammonia was bubbled through the solution. On cooling, the mass solidified and was dissolved in methylene chloride and the resulting solution was washed with water. The methylene chloride solution was dried over magnesium sulfate and the solvent was removed leaving 278.8 g of the crude dihydropyridine. This was dissolved in acetic acid and sodium nitrite (excess) in water was added slowly. The resulting mixture was dissolved in methylene chloride, washed with water and sodium bicarbonate solution and dried over magnesium sulfate. The solvent was removed leaving 195.0 g of the crude pyridine (70% crude yield). The crude product was Kugelrohr distilled to give **8a** as a yellow oil; ^1H nmr (carbon tetrachloride): δ 4.2 (s, 6H, OCH_3), 2.6 (d, 2H, CH_2CH), 2.4 (s, 6H, CH_3), 1.8 (m, 1H, $CH(CH_3)_2$, 0.7, 0.8 (d, 6H, $CH(CH_3)_2$).

Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.26; H, 7.59; N, 5.00.

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

A solution of ethyl 4,4,4-trifluoroacetoacetate (1.8 g, 0.01 mole), methyl β-aminocrotonate (1.1 g, 0.01 mole), paraformaldehyde (0.4 g, 0.013 mole) and triethylamine (3 drops) in ethanol (50 ml) was refluxed for 1 hour. The resulting solution was evaporated and the residue solidified. Recrystallization from methanol/water gave **4a** as a white solid (1.86 g, 0.006 mole, 60%), mp 145.5-146.5°. Concentration of the filtrate gave a second crop (0.6 g); ^1H nmr (acetone-d_6): δ 3.6 (q, 2H, CH_2CH_3), 2.7 (d, 2H, CH_2), 2.6 (t, 1H, CH), 2.9 (s, 3H, OCH_3), 2.2 (m), 1.65 (s), 0.6 (t, 3H, CH_2CH_3); ^{19}F nmr (acetone-d_6): δ -83 (s, CF_3).

Anal. Calcd. for $C_{12}H_{16}F_3NO_5$: C, 46.30; H, 5.18; N, 4.50. Found: C, 46.35; H, 5.20; N, 4.48.

Methyl 5-Methyl-2-(trichloroacetyl)-2-hexenoate (**2a**).

A solution of methyl 4,4,4-trichloroacetoacetate (17.6 g, 0.08 mole), isovaleraldehyde (14.0 g, 0.16 mole), piperidine (*ca* 5 drops) and acetic acid (*ca* 2 drops) in cyclohexane (*ca* 150 ml) was refluxed under a Dean-Stark trap for 2 hours (water layer 1.2 ml; theoretical amount, 1.4 ml). The cyclohexane was removed *in vacuo* and a small amount of piperidine hydrochloride (by nmr) was removed by filtration. The filtrate (22.2 g) was Kugelrohr distilled giving **2a** as a light yellow liquid (18.8 g, 0.066 mole, 82%); ^1H nmr (deuteriochloroform): δ 7.1, 7.7 (2t, 1H, CH = C, *cis* and *trans*), 3.8 (s, 3H, OCH_3), 2.6 (t), 2.2 (t), 1.7 (m, 1H, $CH(CH_3)_2$), 1.0, 0.75 (d, 6H, $CH(CH_3)_2$); ms: m/e 286.

Anal. Calcd. for $C_{10}H_{13}Cl_3O_3$: C, 41.77; H, 4.56; Cl, 36.99. Found: C, 41.82; H, 4.69; Cl, 36.88.

Dimethyl 1,2,3,4-Tetrahydro-1-hydroxy-6-methyl-4-(2-methylpropyl)-1-(trichloromethyl)-3,5-pyridinedicarboxylate (**4b**).

A solution of methyl 5-methyl-2-(trichloroacetyl)-2-hexenoate (95 g, 0.033 mole) and methyl β-aminocrotonate (3.6 g, 0.032 mole) in tetrahydrofuran (50 ml) was refluxed for 16 hours. Analysis (hplc) showed the presence of four major products. The solvent was evaporated on a rotary evaporator and the residue (13.5 g) solidified. Recrystallization from methanol and filtering gave **4b** as a white solid (4.8 g, 0.012 mole, 38%), mp 141.5-143.0°; ^1H nmr (deuteriochloroform): δ 3.8 (s, 3H, OCH_3), 3.7 (s, 3H, OCH_3), 3.3 (m, 3H), 2.35 (s, 3H, CH_3), 1.4 (m, 2H), 0.85 (2d, 6H, $CH(CH_3)_2$); ms: m/e (hplc acetonitrile) 401.

Anal. Calcd. for $C_{15}H_{22}Cl_3NO_5$: C, 44.74; H, 5.52; N, 3.50; Cl, 26.42. Found: C, 44.78; H, 5.52; N, 3.50; Cl, 26.42.

Dimethyl 1,2,3,4-Tetrahydro-6-methyl-4-(2-methylpropyl)-1-oxo-3,5-pyridinedicarboxylate (**7**).

The filtrate from above was concentrated to dryness and the residue was dissolved in methylene chloride. The resulting solution was washed with 10% hydrochloric acid and the methylene chloride was removed on a rotary evaporator. Recrystallization of the residue from methylene chloride/hexane gave **7** as a white solid (1.5 g), mp 125-126°; ^{1}H nmr (deuteriochloroform): δ 3.59 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 2.2 (s, 3H, CH_3), 1.8 (d, 6H, $CH(CH_3)_2$); ms: m/e 283; ^{13}C nmr indicated the presence of a proton at C3 showing the compound had a keto rather than an enol structure.

Anal. Calcd. for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.24; H, 7.49; N, 4.92.

Dimethyl 2-Methyl-4-(2-methylpropyl)-6-(trichloromethyl)-3,5-pyridinedicarboxylate (**6**).

a. From **4b**.

A reaction was carried out as described above. After removal of the tetrahydrofuran, the residue (13.5 g) was dissolved in methylene chloride and phosphorus oxychloride (4.5 g) was added. The solution was refluxed for 4 hours and water (35 ml) was added. Analysis (hplc) of a portion of the methylene chloride layer indicated the presence of two major products with retention times of 15 and 22 minutes. The mixture was separated by preparative hplc (methylene chloride/cyclohexane, Waters® Auto 500) and spectral evidence indicated that the 22 minute eluting material was a dihydropyridine **5**; ^{1}H nmr (carbon tetrachloride): δ 3.55 (s, 3H, OCH_3), 3.4 (s, 3H, OCH_3), 3.1 (m, 3H), 2.15 (s, 3H, CH_3), 0.7 (d, 6H, $CH(CH_3)_2$); ms: m/e 381. The 15 minute eluting material was unstable and a parent peak could not be found. Neither material was stable enough to provide a satisfactory elemental analysis. Sodium nitrite (7.5 g in water) was added to the methylene chloride layer over 2 hours at reflux (42°). The mixture was stirred for 1 hour and the methylene chloride layer was separated and dried (magnesium sulfate). Removal of the methylene chloride on a rotary evaporator left a residue (12.2 g) which contained 2 major products (19 and 22 minutes by hplc *ca* 80:20 by area %). Subsequent to this experiment, it was shown that the 22 minute starting product could be converted into the 15 minute product by refluxing with hydrochloric acid and this could be oxidized (sodium nitrite) to the 19 minute eluting product.

The residue was extracted with 20% ethyl acetate/cyclohexane and eluted through a column of silica gel with 20% ethyl acetate/cyclohexane. Combining fractions containing the 19 minutes eluting product and removal of the solvent on a rotary evaporator gave **6** (10.8 g, 0.028 mole, 88%). The product contained *ca* 5% of the unreacted 22 minute eluting dihydropyridine (by hplc area %). The analytical sample was taken from a middle fraction of the chromatography; ^{1}H nmr (carbon tetrachloride): δ 3.8 (s, 3H, OCH_3), 3.7 (s, 3H, OCH_3), 2.7 (d, 2H, CH_2-CH), 2.5 (s, 3H, CH_3), 1.8 (m, 1H, $CH(CH_3)_2$), 0.85 (d, 6H, $CH(CH_3)_2$); ms: m/e 381.

Anal. Calcd. for $C_{15}H_{18}Cl_3NO_4$: C, 47.08; H, 4.74; N, 3.66; Cl, 27.79. Found: C, 47.19; H, 4.77; N, 3.63; Cl, 27.69.

b. From **8a**.

A solution of **8a**, 2.8 g (10 mmoles), in 75 ml of chlorobenzene was added to a 300 ml autoclave along with 14.3 g (120 mmoles) of thionyl chloride in 20 ml of chlorobenzene. The reaction was then carried out at 120° for 5 hours. The solution was then added to 200 ml of methanol and stirred for 0.5 hour. Water (100 ml) was added and the solution was extracted twice with 100 ml of methylene chloride. The portions were combined, dried over magnesium sulfate, and concentrated to leave 2.69 g of **6**. The ^{1}H nmr and ms were identical with the product from part a.

c. From **16a**.

A solution of **16a**, 3.0 g (8.6 mmoles), in 60 ml of methylene chloride with 5.5 g of aluminum chloride, was stirred at 30° for several hours. After ^{19}F nmr monitoring had indicated nearly complete reaction, the mixture was poured into 37% hydrochloric acid on ice, and further extracted with methylene chloride. Analysis (hplc) with 1.5% ethyl acetate in cyclohexane gave in fractions 2-4, 1.2 g (36%) of **6**, identical in all respects with material derived from preparation a.

Dimethyl 2,6-Bis-(dichloromethyl)-3,5-pyridinedicarboxylate (**9**).

To 17.6 g (78.2 mmoles) of **8b** dissolved in 200 ml of benzotrifluoride in a 500 ml 3-necked round bottomed flask fitted with an overhead stirrer was added 28.3 g (238 mmoles) of thionyl chloride and 64.2 g (476 mmoles) of sulfuryl chloride. The clear yellow solution was then heated at 75°. After 5 hours, it became necessary to add an additional 5 ml of sulfuryl chloride to prohibit sulfur dichloride formation, which was indicated by a deep reddish color. After a total of 10 hours, the reaction had stopped, according to hplc. The solution was then washed with water, separated, and dried over magnesium sulfate. After removing the solvent, 27.5 g of crude product remained. This was then dissolved in 80 ml of hot methanol and 20 ml of water was added. After stirring an additional 1.5 hours, the pure white crystalline **9** was filtered (13.0 g, 46%); ^{1}H nmr (carbon tetrachloride): δ 8.8 (s, 1H, 4-H), 7.85 (s, 2H, $CHCl_2$), 4.0 (s, 6H, OCH_3); ms: m/e 359.

Anal. Calcd. for $C_{11}H_9Cl_4NO_4$: C, 36.59; H, 2.51; N, 3.88; Cl, 39.29. Found: C, 36.54; H, 2.53; N, 3.86; Cl, 39.39.

Dimethyl 2-(Dichloromethyl)-6-(trichloromethyl)-3,5-pyridinedicarboxylate (**10**).

Compound **8b** (4.5 g, 20 mmoles) was dissolved in 125 ml of benzotrifluoride and added to a 300 ml autoclave along with 7.3 g (61 mmoles) of thionyl chloride and 16.6 g (126 mmoles) of sulfuryl chloride in 25 ml of benzotrifluoride. The reaction was carried out at 120° for 5.5 hours. The solution was then washed with water, separated and dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue was recrystallized from methanol. This produced **10** (3.95 g, 50%); ^{1}H nmr (carbon tetrachloride): δ 8.4 (s, 1H, 4-H), 7.8 (s, 1H, $CHCl_2$), 4.0 (s, 3H, OCH_3), 3.9 (s, 3H, OCH_3); ms: m/e 393.

Anal. Calcd. for $C_{11}H_8Cl_5NO_4$: C, 33.41; H, 2.03; N, 3.54; Cl, 44.88. Found: C, 33.44; H, 2.05; N, 3.51; Cl, 44.78.

Trimethyl 2-(Dichloromethyl)-3,5,6-pyridinetricarboxylate (**11**).

Material **9** (9.0 g, 25 mmoles) was dissolved in 75 ml of chlorobenzene and added to a 300 ml autoclave along with 1.7 g (14 mmoles) of thionyl chloride and 3.4 g (25 mmoles) of sulfuryl chloride in 25 ml of chlorobenzene. The reaction was run at 109° for 6 hours. The solution was returned to the autoclave along with an additional 1.7 g (14 mmoles) of thionyl chloride and 3.4 g (25 mmoles) of sulfuryl chloride in 10 ml of chlorobenzene and run at 110° for 5 hours. The solution was again returned to the autoclave, but this time with 6.1 g (51 mmoles) of thionyl chloride and 13.9 g (102 mmoles) of sulfuryl chloride. It was then heated at 113° for 4.5 hours. The solution was returned to the autoclave once more with 6.2 g (52 mmoles) of thionyl chloride and 13.4 g (100 mmoles) of sulfuryl chloride and run at 120° for 5.25 hours. It was then washed with water, dried over magnesium sulfate and concentrated. Methanol was added to give a precipitate. This was filtered and recrystallized from methanol to give fine, white **11** (2.9 g, 35%), mp, 109-110°; ^{1}H nmr (carbon tetrachloride): δ 8.7 (s, 1H, 4-H), 7.8 (s, 1H, $CHCl_2$), 4.00, 3.98, 3.95 (3s, 9H, OCH_3); ms: m/e 335.

Anal. Calcd. for $C_{12}H_{11}Cl_2NO_6$: C, 42.88; H, 3.30; N, 4.17; Cl, 21.10. Found: C, 42.93; H, 3.31; N, 4.14; Cl, 21.04.

Procedures relating to the preparation of materials **12-a-g** and **16a,b** are decribed elsewhere [1].

Dimethyl 2-(Dichloromethyl)-4-methyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**13a**).

Starting material, **12a** (6.5 g, 20 mmoles) was dissolved in 60 ml of methylene chloride and 6 g of fresh aluminum chloride added, with the initial temperature controlled by ice cooling. After two days stirring at room temperature, the mixture consisted of product and chlorolactone,

14a. Washing with 10% hydrochloric acid and methylene chloride extraction gave upon layer separation and evaporation a residue which was triturated with ether. This gave solid chlorolactone **14a**. Recrystallization of the ether extract from methanol gave a mixture. This was subjected to hplc with 28% methylene chloride in cyclohexane to give 1.6 g (22%) product from fractions 6-11. Recrystallization from 2-propanol gave a white solid, mp 117.5-118°; ^{1}H nmr (deuteriochloroform): δ 2.3 (s, 3H, CH_3), 3.95 (d, 6H, 2 OCH_3), 6.85 (s, 1H, $CHCl_2$); ^{19}F nmr: δ -64.9 (s, CF_3); ms: (high resolution ei) m/e Calcd: 358.9939. Found: 358.9956 (2 Cl).

Anal. Calcd. for $C_{12}H_{10}Cl_2F_3NO_4$: C, 40.02; H, 2.80; N, 3.89. Found: C, 40.20; H, 2.87; N, 3.83.

Dimethyl 2-(Dichloromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**13b**).

Material **12b**, 4 g (11 mmoles) was dissolved in 100 ml of methylene chloride with 4 g of dry aluminum chloride. After seven hours, glc indicated mostly product with small contamination by chlorolactone **14b** and starting material **12b**. The reaction mixture was poured into ice mixed with 37% hydrochloric acid, and the well stirred mixture extracted with additional methylene chloride. The separated organic solution was evaporated under vacuum to give 4.5 g of residue. This material was Kugelrohr distilled and the fraction between 120-160° (1 mm Hg) collected as 3.6 g of product (81%). Recrystallization of a portion from cold methanol gave a product with mp 60-61°; ^{1}H nmr (deuteriochloroform): δ 0.8 (d, 6H, $CH(CH_3)_2$), 1.75 (h, 1H, $CH(CH_3)_2$), 2.65 (d, 2H, CH_2), 3.95 (d, 6H, 2 OCH_3), 6.95 (s, 1H, $CHCl_2$).

Anal. Calcd. for $C_{15}H_{16}Cl_2F_3NO_4$: C, 44.80; H, 4.01; Cl, 17.63; N, 3.48. Found: C, 44.94; H, 4.03; Cl, 17.52; N, 3.46.

Methyl 6-(Dichloromethyl)-4-(2-methylpropyl)-2-(trifluoromethyl)-3-pyridinecarboxylate (**13c**).

Starting material, **12c**, (6.2 g, 20 mmoles) was dissolved in 75 ml of nitromethane with 5 g of aluminum chloride and refluxed for 0.5 hour. Washing with 10% hydrochloric acid solution and methylene chloride extraction gave after solvent separation and evaporation, a dark oil. Kugelrohr distillation at 120-150° (1.5 mm Hg) gave 5.2 g (100% glc assay) of distillate (76%) and 1.5 g of residue.

A similar reaction in methylene chloride at room temperature for *ca* 4 hours gave a nearly complete reaction. From 4.9 g (15.7 mmoles) of **12c** was obtained 5.1 g (94%) of distillate and 0.1 g of residue. Further purification could be effected by hplc with 0.5% ethyl acetate in cyclohexane to give fractions 1-4 containing the product, Kugelrohr bp 120-140° (1.5 mm Hg), colorless oil; n_D^{25} 1.4783; ^{1}H nmr (deuteriochloroform): δ 0.9 (d, 6H, $CH(CH_3)_2$), 1.9 (h, 1H, $CH(CH_3)_2$), 2.6 (d, 2H, CH_2), 3.95 (s, 3H, OCH_3), 6.7 (s, 1H, $CHCl_2$), 7.85 (s, 1H, H-5); ^{19}F nmr: (s, CF_3).

Anal. Calcd. for $C_{13}H_{14}Cl_2F_3NO_2$: C, 45.37; H, 4.10; Cl, 20.60, N, 4.07. Found: C, 45.30; H, 4.13; Cl, 20.54; N, 4.04.

S,S-Dimethyl 2-(Dichloromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarbothioate (**13d**).

The starting material, **12d**, (2.3 g, 5.7 mmoles), was dissolved in 50 ml of methylene chloride and 2.3 g of aluminum chloride was added. Several hours stirring failed to convert all of the starting material to product, therefore 2 g of the metal halide was added to complete the reaction. The reaction appeared to go very cleanly by glc. The reaction mixture was poured into 37% hydrochloric acid solution diluted with ice and methylene chloride. The organic phase was separated, dried with magnesium sulfate, filtered and vacuum treated to remove the solvent, leaving a solid which was recrystallized from heptane to give crystals, 0.9 g, (36%), mp 123-125°; ^{1}H nmr (deuteriochloroform): δ 0.87 (d, 6H, $CH(CH_3)_2$), 2.0 (h, 1H, $CH(CH_3)_2$), 2.70 and 2.73 (2s, 6H, 2 SCH_3), 2.87 (d, 2H, CH_2), 6.95 (s, 1H, $CHCl_2$); ^{19}F nmr: (s, CF_3).

Anal. Calcd. for $C_{15}H_{16}Cl_2F_3NO_2S_2$: C, 41.48; H, 3.71; Cl, 16.32; N, 3.22; S, 14.77. Found: C, 41.52; H, 3.75; Cl, 16.38; N, 3.19; S, 14.68.

S,S-Dimethyl 4-(Cyclopropylmethyl)-2-(dichloromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarbothioate (**13e**).

The starting material, **12e**, (5 g, 12.5 mmoles), was dissolved in 50 ml of methylene chloride with 5 g of fresh, dry aluminum chloride. After stirring several hours, sampling indicated a complete and clean reaction. The reaction mixture was poured into a mixture of 37% hydrochloric acid and ice with stirring, with extraction with additional methylene chloride. After layer separation, the material was vacuum treated to give 5.3 g of brown solid. Recrystallization from methylcyclohexane gave 2.5 g (46%) of product, mp 143-147°; ^{1}H nmr (deuteriochloroform): δ 0-1.2 (multiplets, cyclopropyl), 2.50 and 2.55 (2s, 6H, 2 SCH_3), 2.65 (d, 2H, CH_2), 6.75 (s, 1H, $CHCl_2$); ^{19}F nmr: (s, CF_3).

Anal. Calcd. for $C_{15}H_{14}Cl_2F_3NO_2S_2$: C, 41.67; H, 3.26; Cl, 16.40; N, 3.24. Found: C, 41.84; H, 3.32; Cl, 16.48; N, 3.22.

Diethyl 2-(Dichloromethyl)-4-methyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**13f**).

The starting material **12f** (17.6 g, 50 mmoles) was charged into a one neck 500 ml flask and 200 ml of methylene chloride was added, followed by 17 g of fresh, dry aluminum chloride with magnetic stirring. Stirring at room temperature for three days in the closed vessel gave 85% completion of the reaction, then 5.0 g of aluminum chloride was added, and the mixture was stirred another 24 hours. The mixture was poured into 37% hydrochloric acid diluted with ice and methylene chloride. After extraction, phase separation and organic solvent removal by vacuum evaporation provided the oily residue which weighed 15.4 g. Kugelrohr distillation at 135-175° (1.5 mm Hg) gave 1.8 g of residue and 13.3 g (69%) of yellow oil, which slowly formed crystals. A portion was recrystallized from cold heptane, mp 42.5-45.5°; ^{1}H nmr (deuteriochloroform): δ 1.3 (2 t, 6H, 2 CH_3CH_2), 2.42 (s, 3H, CH_3), 4.55 (2 q, 4H, 2 CH_3CH_2), 7.0 (s, 1H, $CHCl_2$); ^{19}F nmr: (s, CF_3).

Anal. Calcd. for $C_{14}H_{14}Cl_2F_3NO_4$: C, 43.32; H, 3.64; Cl, 18.27; N, 3.61. Found: C, 43.34; H, 3.65; Cl, 18.20; N, 3.60.

2-(Dichloromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)pyridine (**13g**).

The starting material **12g** (6 g, 23.7 mmoles) was mixed with 6 g of aluminum chloride in methylene chloride and refluxed. Examination after 1.5 hours revealed a mixture of the title compound and **15** (see below). After washing with 10% hydrochloric acid and workup, the residue was examined by chromatography and found difficult to separate. Consequently the residue was distilled by a short path distillation apparatus to give 0.5 g (7.4%) as a center cut at 110° (1 mm Hg); n_D^{25} 1.4707; ^{1}H nmr (deuteriochloroform): δ 0.9 (d, 6H, $CH(CH_3)_2$), 2.0 (h, 1H, $CH(CH_3)_2$), 2.7 (d, 2H, CH_2), 6.8 (s, 1H, $CHCl_2$), 7.5 and 7.8 (2s, 2H, H-3 and H-5); ^{19}F nmr: (s, CF_3); ms: glc/ci m/e, 285 (2 Cl).

Anal. Calcd. for $C_{11}H_{12}Cl_2F_3N$: C, 46.18; H, 4.23; Cl, 24.78; N, 4.90. Found: C, 46.23; H, 4.23; Cl, 24.71; N, 4.90.

Methyl 7-Chloro-5,7-dihydro-4-methyl-5-oxo-2-(trifluoromethyl)furo-[3,4-*b*]pyridine-3-carboxylate (**14a**).

The starting material **12a** (16.4 g, 50 mmoles) was dissolved in 100 ml of nitromethane and refluxed with aluminum chloride (fresh, dry reagent of this latter material should be used, otherwise poor reaction and gel formation occurs). After reflux for 1 hour, the cooled material was poured into ice/10% hydrochloric acid and extracted with methylene chloride. The solution was then filtered through filter-aid, and the organic solvent vacuum evaporated to give 16 g of residue. Kugelrohr distillation at 125-170° (1.5 mm) gave 14.1 g of distillate and 1.6 g of residue. The partially crystallized oil was filtered (filtrate contained 3.8 g of **12a**) and purification of the solid to the lactone effected by trituration with ether and recrystallization from 2-propanol provided 3.8 g (27%) of white crystals, mp 139-140°; ^{1}H nmr (deuteriochloroform): δ 2.7 (s, 3H, CH_3), 3.9 (s, 3H, OCH_3), 7.0 (s, 1H, CHCl); ^{19}F nmr: (s, CF_3); ms: m/e glc/ci 309 (1 Cl).

Anal. Calcd. for $C_{11}H_7ClF_3NO_4$: C, 42.67; H, 2.28; Cl, 11.45; N, 4.52. Found: C, 42.75; H, 2.36; Cl, 11.43; N, 4.50.

Methyl 7-chloro-5,7-dihydro-4-(2-methylpropyl)-5-oxo-2-(trifluoromethyl)-furo[3,4-*b*]pyridine-3-carboxylate (**14b**).

The starting material **12b** (7.4 g, 20 mmoles), was dissolved in *ca* 75 ml of nitromethane with 5 g of fresh, dry aluminum chloride. The mixture was heated to reflux for 0.5 hour, then permitted to stand at room temperature overnight. Both glc and ^{19}F nmr indicated complete conversion to the chlorolactone. Washing with 10% hydrochloric acid and extraction with methylene chloride gave after Kugelrohr distillation at 120-160° (1.2 mm Hg), 6.5 g of distillate at 93.3% assay (86%). To purify the oil, 3.2 g was subjected to hplc with 1.5% ethyl acetate in cyclohexane. Fractions 6-8 were collected as the product after Kugelrohr distillation; n_D^{25} 1.4905; ^1H nmr (deuteriochloroform): δ 0.97 (d, 6H, $CH(CH_3)_2$), 2.0 (h, 1H, $CH(CH_3)_2$), 3.08 (d, 2H, CH_2), 4.0 (s, 3H, OCH_3), 7.15 (s, 1H, CHCl); ^{19}F nmr: (s, CF_3).

Anal. Calcd. for $C_{14}H_{13}ClF_3NO_4$: C, 47.81; H, 3.73; Cl, 10.08; N, 3.98. Found: C, 47.82; H, 3.73; Cl, 10.00; N, 3.95.

1-(Dichloromethyl)-4-(2-methylpropyl)-6-(trichloromethyl)pyridine (**15**).

The reaction product, distilled as described for **13g** gave 0.3 g (3.8%) as the middle cut, at 120° (1 mm Hg); n_D^{25} 1.5399; ^1H nmr (deuteriochloroform): δ 1.0 (d, 6H, $CH(CH_3)_2$), 2.0 (h, 1H, $CH(CH_3)_2$), 2.7 (d, 2H, CH_2), 6.8 (s, 1H, $CHCl_2$), 7.7 and 7.9 (2s, 2H, H-3 and H-5); ^{19}F nmr: no absorptions observed; ms: m/e, glc/ci 333 (5 Cl).

Anal. Calcd. for $C_{11}H_{12}Cl_5N$: C, 39.38; H, 3.61; Cl, 52.84; N, 4.18. Found: C, 39.40; H, 3.64; Cl, 52.76; N, 4.12.

Methyl 7,7-Dichloro-5,7-dihydro-4-(methylpropyl)-5-oxo-2-(trichloromethyl)furo[3,4-*b*]pyridine-3-carboxylate (**17**).

The starting material, **16b** (3.0 g, 7 mmoles) was dissolved in *ca* 50 ml of methylene chloride with 6 g of aluminum chloride. The mixture was stirred for 1.5 days, then poured into ice/20% hydrochloric acid and extracted with additional methylene chloride. After organic solvent removal, the residue crystallized. This was recrystallized from cold methanol to give 1.9 g. This material was separated on the Chromatotron with 1.8% ethyl acetate in cyclohexane. Fractions 2 and 3 gave **17**, *ca* 0.6 g, (20%) mp (recrystallized unchanged from methanol) 118->140°; Fourier transform ir revealed this chemical probably exists as ring/chain tautomers on heating or glc. The acid chloride and lactone carbonyl groups unfortunately absorb in the same region (1800-1700 cm^{-1}). The C-Cl band of an acid chloride is usually found near 800 cm^{-1}, while C-O-C are found in the 1100 and 900 cm^{-1} region. A high temperature (295° gas phase) spectrum of **17** revealed a strong band at 815 cm^{-1} indicative of the acid chloride C-Cl, with no strong band in the 975 cm^{-1} region. On the other hand, a room temperature ir (potassium bromide dispersed) revealed a strong complex of bands at 970 cm^{-1} indicative of the lactone C-O-C and a much diminished 815 cm^{-1} absorption for the acid chloride; ^1H nmr (deuteriochloroform): 30°, δ 0.9 (d, 6H, $CH(CH_3)_2$), 2.0 (h, 1H, $CH(CH_3)_2$), 3.0 (d, 2H, CH_2), 4.0 (s, 3H, OCH_3); ^{19}F nmr: no absorptions observed; ms: m/e glc/ci 433 (5 Cl).

Anal. Calcd. for $C_{14}H_{12}Cl_5NO_4$:C, 38.61; H, 2.78; Cl, 40.70; N, 3.22. Found: C, 38.70; H, 2.80; Cl, 40.77; N, 3.19.

Dimethyl 4-(2-Methylpropyl)-2,6-bis(trichloromethyl)-3,5-pyridinedicarboxylate (**18**).

Continuing the preparation described for isolation of **17**, fractions 5 and 6 gave **18** from methanol, mp 125-126°; ^1H nmr (deuteriochloroform): δ 0.8 (d, 6H, $CH(CH_3)_2$), 1.9 (h, 1H, $CH(CH_3)_2$), 2.7 (d, 2H, CH_2), 3.9 (s, 6H, OCH_3); ^{19}F nmr: no absorptions observed; ms: m/e glc/ci 483 (6 Cl).

Anal. Calcd. for $C_{15}H_{15}Cl_6NO_4$: C, 37.07; H, 3.11; Cl, 43.77; N, 2.88. Found: C, 37.19; H, 3.13; Cl, 43.57; N, 2.80.

Methyl 7,7-Dichloro-5,7-dihydro-4-(2-methylpropyl)-5-oxo-2-methylfuro-[3,4-*b*]pyridine-3-carboxylate (**19**).

Fractions 7 and 8 from hplc described in method c for **6** were evaporated, then Kugelrohr distilled at 180-210° (1.5 mm Hg) to give 0.2 g of solid (7%), mp 76-78°; ^1H nmr (deuteriochloroform): δ 0.8 (d, 6H, $CH(CH_3)_2$), 1.9 (h, 1H, $CH(CH_3)_2$), 2.6 (s, 3H, CH_3), 2.85 (d, 2H, CH_2), 3.9 (s, 3H, OCH_3); ^{19}F nmr: no absorptions observed; ^{13}C (proton coupled) δ 22 (q, 1C, CH_3), 23 (q, 2C, $CH(CH_3)_2$), 29 (d, 1C, CH), 37 (t, 1C, CH_2), 53 (q, 1C, OCH_3), 103 (s, 1C, CCl_2), 112, 132, 151, 161, 164, 165, 167 (7s, 7C, sp^2C); ms: glc/ci m/e 331 (2 Cl).

Anal. Calcd. for $C_{14}H_{15}Cl_2NO_4$: C, 50.62; H, 4.55; Cl, 21.34; N, 4.22. Found: C, 50.71; H, 4.57; Cl, 21.25; N, 4.21.

Dimethyl 4-(2-Methylpropyl)-2-(trichloromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**20b**).

A solution was prepared by adding 4.0 g (10 mmoles) of **13b** and 2.6 g (11 mmoles) of hexachloroethane to 45 ml of tetrahydrofuran. After cooling to -30°, 11 mmoles of lithium bis(trimethylsilyl)amide was added dropwise (as a 1*M* solution in tetrahydrofuran). The mixture was stirred 15 minutes after the addition, then permitted to warm to room temperature after removal of the cooling bath. The contents of the reaction flask were poured into 150 ml of cold, 2% hydrochloric acid, and extracted with methylene chloride. The organic layer was separated, the organic solvent evaporated to 90° (1 mm Hg). The 4.0 g of residue was Kugelrohr distilled at 140-175° (1.5 mm Hg) to give 3.4 g (78%) of product; recrystallization from hexane gave crystals mp 89.5-90°; ^1H nmr (deuteriochloroform): δ 0.85 (d, 6H, $CH(CH_3)_2$), 1.9 (h, 1H, $CH(CH_3)_2$), 2.75 (d, 2H, CH_2), 3.95 (s, 6H, OCH_3); ^{19}F nmr: (s, CF_3); ms: m/e glc/ci 435 (3 Cl).

Anal. Calcd. for $C_{15}H_{15}Cl_3F_3NO_4$: C, 41.26; H, 3.46; Cl, 24.36; N, 3.21. Found: C, 40.81; H, 3.43; Cl, 23.98; N, 3.13.

Methyl 6-(Trichloromethyl)-4-(2-methylpropyl)-2-(trifluoromethyl)-3-pyridinecarboxylate (**20c**).

The starting material **13c** (3.5 g, 10 mmoles) having 90% assay was placed in *ca* 40 ml of tetrahydrofuran with 2.6 g (11 mmoles) of hexachloroethane. To this stirred mixture at -30° was added 1.2 g (11 mmoles) of potassium *t*-butoxide. After addition, the mixture was stirred at -30° for 0.5 hour, then allowed to warm to room temperature. After washing with dilute hydrochloric acid and extraction with methylene chloride, the layers were separated, and the organic portion evaporated at 90° (1 mm Hg). The 3.1 g of residue was subjected to hplc with 7.5% methylene chloride in cyclohexane to give product fractions 3 and 4. Kugelrohr distillation at 120-140° (1.5 mm Hg) gave 1.4 g (37%) of colorless oil; n_D^{25} 1.4856; ^1H nmr (deuteriochloroform): δ 1.0 (d, 6H, $CH(CH_3)_2$), 1.9 (h, 1H, $CH(CH_3)_2$), 2.65 (d, 2H, CH_2), 4.0 (s, 3H, OCH_3), 8.1 (s, 1H, H-5); ^{19}F nmr: (s, CF_3).

Anal. Calcd. for $C_{13}H_{13}Cl_3F_3NO_2$: C, 41.24; H, 3.46; Cl, 28.09; N, 3.70. Found: C, 41.27; H, 3.46; 28.01; N, 3.69.

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