Note: The chlorinations of **11**, **12**, **13**, **14**, and **15** were performed in the manner as described for **3**. These were subsequently hydrolyzed to their respective pyridinemethanols in the manner as described for **4**. Analytically pure samples of the chloromethyl intermediates were prepared by chlorination of the pyridinemethanols by thionyl chloride; a representative procedure is listed for **11a**. The yields for compounds not recrystallized, distilled, or purified by chromatography are reported as approximate.

10,10-Bis[(2-fluoro-4-pyridinyl)methyl)]-9(10H)-anthracenone (1) ^{1}H NMR (399.7 MHz, DMSO-d_6): 8.42 (dd, $J_{14,13}$ = 7.7 Hz, $J_{14,12}$ = 0.9 Hz, 2H, C(=O)CCC**H**), 7.95 (dd, $J_{11,12}$ = 7.7 Hz, $J_{11,13}$ = 1.5 Hz, 2H, C(=O)C=C**H**), 7.93 (ddd, $J_{13,14}$ = 7.7 Hz, $J_{13,12}$ = 7.7 Hz, $J_{13,11}$ = 1.5 Hz, 2H, C(=O)C=CHCH=C**H**), 7.65 (d, $J_{6,5}$ = 5.2 Hz, 2H, NC**H**), 7.53 (ddd, $J_{12,13}$ = 7.7 Hz, $J_{12,11}$ = 7.7 Hz, $J_{12,14}$ = 0.9 Hz, 1H, C(=O)C=CHC**H**), 6.11 (ddd, $J_{5,6}$ = 5.2 Hz, $J_{5,3}$ = 1.4 Hz, $J_{5,F}$ = 2.3 Hz, 2H, NCH=C**H**), 5.92 (dd, $J_{3,5}$ = 1.4 Hz, $J_{3,F}$ = 1.3 Hz, 2H, C(F)C**H**), 3.95 (s, 4H, C**H$_2$**); ^{13}C NMR (DMSO): 181.7 (**C**=O), 162.3 (d, J = 235.0 Hz, **C**F)), 152.1 (d, J = 7.6 Hz, CH$_2$**C**=CH), 146.4 (d, J = 16.0 Hz, N**C**H), 144.1 (C(=O)C**C**), 134.0 (C(=O)C=CHCH=**C**H), 131.7 (C(=O)**C**), 128.5 (C(=O)CC**C**H), 128.0 (C(=O)C=CH**C**H), 126.5 (C(=O)C=**C**H), 122.6 (NCH=**C**H), 109.7 (d, J = 37.4 Hz, C(F)**C**H), 47.9 (CH$_2$**C**CH$_2$), 47.5 (d, J = 2.3 Hz, **C**H$_2$);

4-(Chloromethyl)-2-fluoropyridine (4) IR (neat) 3068, 1614, 1574, 1554, 1479, 1404, 1289, 1144, 959, 829, 769, 739, 719 cm^{-1}.

4-(Dichloromethyl)-2-fluoropyridine (5)[1] After **3** (20.00 g, 176.4 mmol) had been chlorinated and hydrolyzed as previously described, the reaction mixture was heated until 150 mL of distillate had collected. The distillate was extracted with heptane (100 mL) and washed twice with water. After drying ($MgSO_4$), the solution was concentrated *in vacuo* to 4.10 g (13% crude yield) of colorless oil. ^{1}H NMR (300.0 MHz, $CDCl_3$) 8.30 (d, J = 5.4 Hz,

1H), 7.37-7.39 (m, 1H), 7.15 (s, 1H), 6.66 (s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) 163.9 (d, J = 240.2 Hz), 153.3 (d, J = 8.1 Hz), 148.7 (d, J = 15.6 Hz), 118.6 (d, J = 4.6 Hz), 107.1 (d, J = 39.8 Hz), 68.4 (d, J = 4.0 Hz). The elemental analysis was unacceptable. Copies of the ^1H and ^{13}C NMR spectra are included.

2-Fluoro-4-pyridinemethanol, 4-methylbenzenesulfonate (7) IR (KBr) 3099, 3082, 3049, 3021, 3010, 2987, 2982, 2964, 2932, 1620, 1572, 1558, 1488, 1458, 1413, 1350, 1186, 1147, 988, 964, 853, 773, 756, 529, 508 cm^{-1}.

2-Fluoro-4-(iodomethyl)-pyridine (8)[1] A solution of 36.0 g (175 mmol) of **7**, sodium iodide (39.4 g, 263 mmol) and acetone (1.0 L) was stirred for 2 h at 5-20 °C and at 30 °C for 30 min. The solution was concentrated *in vacuo* and the resulting oil was mixed with water (300 mL), heptane (50 mL), EtOAc (50 mL), and saturated sodium thiosulfate (5 mL). The organic phase was separated and the aqueous layer further extracted with 1:1 heptane/EtOAc (100 mL). The combined organic extracts were dried over $MgSO_4$ and the solution concentrated *in vacuo* to produce 40.3 g (97%) of reddish orange oil (99.8 LC area %). The ^1H NMR spectrum did not display any impurities. ^1H NMR (300.0 MHz, $CDCl_3$): 8.12 (d, J = 5.1 Hz, 1H), 7.13 (d, J = 5.1 Hz, 1H), 6.88 (s, 1H), 4.31 (s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): 163.8 (d, J = 237.9 Hz), 153.5 (d, J = 8.2 Hz), 148.1 (d, J = 15.5 Hz), 121.3 (d, J = 4.6 Hz), 109.2 (d, J = 38.0 Hz), 46.6; ^{19}F NMR (376 MHz, $CDCl_3$): -68.1; MS: m/e 238(M+H). The compound was too unstable to be analyzed for elemental composition. Copies of ^1H and ^{13}C NMR spectra are included for proof of purity.

1,2-Di-(2-fluoro-4-pyridyl)ethylene (10) A solution of 1.6 M potassium *t*-butoxide in THF (1.6 mL, 2.6 mmol) was added over 10 min to a solution of **7** (0.25 g, 1.2 mmol), sodium iodide (0.40 g, 2.7 mmol), and THF (30 mL). The solution was stirred for another 90 min and diluted with water (50 mL) and ethyl acetate (20 mL). The layers were separated and the

organic phase washed with water. The solution was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from IPA (5 mL) to yield 65 mg of yellow solids (50%). mp 240 °C (dec). ^1H NMR (300.0 MHz, DMSO-d_6): 8.27 (d, J = 5.3 Hz, 1H), 7.65 (s, 1H), 7.56 (d, J = 1.5 Hz), 7.38 (s, 1H). ^{13}C NMR (DMSO-d_6): 163.9 (d, J = 234.2 Hz), 149.3 (d, J = 8.6 Hz), 148.2 (d, J = 15.6 Hz), 130.9 (d, J = 3.5 Hz), 119.9 (d, J = 3.5 Hz), 106.7 (d, J = 38.3 Hz). Anal. Calcd for $C_{12}H_8F_2N_2$: C, 66.06; H, 3.69; N, 12.80. Found: C, 66.00; H, 4.10; N, 12.65.

3-(Chloromethyl)-2-fluoropyridine (11a) Alcohol **11b** (2.00 g, ~15.7 mmol) was added dropwise over 5 min to a flask of thionyl chloride (10 mL) cooled in ice. The bath was removed after 5 min. After another 45 min, the solution was concentrated *in vacuo*. The residue was quenched with saturated $NaHCO_3$ and extracted into ethyl acetate. The extracts were washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on 60 g of silica gel (EtOAc:hexane 1:4) to produce 1.72 g (~75%) of clear oil (100 LC area %; clean by ^1H NMR spectroscopy). ^1H NMR (300.0 MHz, $CDCl_3$): 8.20 (br d, J = 4.8 Hz, 1H), 7.92-7.80 (m, 1H), 7.25-7.20 (m, 1H), 4.63 (s, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$) 160.99 (d, J = 240.4 Hz), 147.70 (d, J = 14.5 Hz), 141.11 (d, J = 4.1 Hz), 121.80 (d, J = 4.2 Hz), 119.78 (d, J = 29.6 Hz), 38.72. ^{19}F NMR (282.2 MHz, $CDCl_3$): -72.04. Anal. Calcd for C_6H_5ClFN: C, 49.51; H, 3.46; N, 9.62; F, 13.05; Cl, 24.36. Found: C, 49.32; H, 3.48; N, 9.68; F,13.14; Cl, 24.08.

2-Fluoro-3-pyridinemethanol (11b)[2] Isolated in ~48% overall yield from **11** as a yellow oil after column chromatography (EtOAc). ^1H NMR (300.0 MHz, $CDCl_3$): 8.11 (d, J = 4.4 Hz, 1H), 8.0-7.8 (m, 1H), 7.3-7.2 (m, 1H), 4.77 (s, 2H), 2.72 (v br s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) 160.7 (d, J = 239.6 Hz), 145.7 (d, J = 13.8 Hz), 139.4 (d, J = 4.8 Hz), 123.2 (d, J = 29.0 Hz), 121.5 (d, J = 4.1 Hz), 57.8 . ^{19}F NMR (282.2 MHz, $CDCl_3$): -73.9 . Elemental

analysis was unacceptable despite repeated and varied chromatography. Copies of the ^{1}H and ^{13}C NMR spectra are included for proof of purity.

5-(Chloromethyl)-2-fluoropyridine (12a) Isolated in ~53% yield as a colorless oil after column chromatography (hexane:EtOAc 4:1). ^{1}H NMR (300.0 MHz, $CDCl_3$): 8.23 (d, J = 2.1 Hz, 1H), 7.9-7.8 (m, 1H), 6.96 (dd, J = 8.4, 2.9 Hz, 1H), 4.59 (s, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 163.4 (d, J = 241.0 Hz), 147.4 (d, J = 15.2 Hz), 141.5 (d, J = 8.2 Hz), 109.8 (d, J = 38.0 Hz), 42.1 . ^{19}F NMR (282.2 MHz, $CDCl_3$): -68.3; Anal. Calcd for C_6H_5ClFN: C, 49.51; H, 3.46; N, 9.62; F, 13.05; Cl, 24.36. Found: C, 49.34; H, 3.41; N, 9.58; F, 13.15; Cl, 24.35.

2-Fluoro-5-pyridinemethanol (12b)[3] Isolated in ~47% overall yield from **12** as a yellow oil. ^{1}H NMR (300.0 MHz, $CDCl_3$): 8.17 (d, J = 2.2 Hz, 1H), 7.9-7.8 (m, 1H), 7.10 (dd, J = 8.4, 2.6 Hz, 1H), 4.72 (s, 2H), 2.52 (br s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 163.1 (d, J = 239.6 Hz), 146.0 (d, J = 14.6 Hz), 140.4 (d, J = 8.2 Hz), 134.1 (d, J = 4.2 Hz), 109.4 (d, J = 37.3 Hz), 61.6 . ^{19}F NMR (282.2 MHz, $CDCl_3$): -70.4 . Anal. Calcd for C_6H_6FNO: C, 56.69; H, 4.76; F, 14.95; N, 11.02. Found: C, 56.54; H, 4.84; F, 14.60; N, 11.09 .

6-(Chloromethyl)-2-fluoropyridine (13a) Isolated in ~82% yield as a red oil. ^{1}H NMR (300.0 MHz, $CDCl_3$): 7.83 (dd, J = 15.6, 7.8 Hz, 1H), 7.37 (dd, J = 7.2, 2.0 Hz, 1H), 6.90 (dd, J = 8.4, 2.7 Hz, 1H), 4.60 (s, 2). ^{13}C NMR (75.4 MHz, $CDCl_3$): 162.8 (d, J = 241.2 Hz), 155.4 (d, J = 10.3 Hz), 142.0 (d, J = 7.6 Hz), 119.9 (d, J = 4.1 Hz), 109.0 (d, J = 36.8 Hz), 45.5 . Anal. Calcd for C_6H_5ClFN: C, 49.51; H, 3.46; Cl, 24.35; F, 13.05. Found: C, 49.60; H, 3.54; Cl, 24.58; F, 13.33.

2-Fluoro-6-pyridinemethanol (13b) Isolated in ~55% overall yield from **13** as an orange oil. ^{1}H NMR (300.0 MHz, $CDCl_3$): 7.79 (dd, J = 15.6, 8.1 Hz, 1H), 7.23 (dd, J = 7.5, 2.0 Hz,

1H), 6.83 (dd, J = 8.1, 2.0, 1H), 4.73 (br s, 2H), 3.52 (br s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 163.1 (d, J = 241.2 Hz), 159.1 (d, J = 12.1 Hz), 141.7 (d, J = 7.5 Hz), 117.5 (d, J = 4.1 Hz), 107.7 (d, J = 36.3 Hz), 64.1 . Anal. Calcd for C_6H_6FNO: C, 56.69; H, 4.76; F, 14.95. Found: C, 56.72; H, 4.68; F, 15.09.

6-(Dichloromethyl)-2-fluoropyridine (13c) A solution of **13** (5.00 g, 44.1 mmol), N-chlorosuccinimide (8.90 g, 66.7 mmol), benzoyl peroxide (0.22 g, 0.91 mmol) and acetonitrile (25 mL) were refluxed for 100 min. Another 8.90 g of NCS was added and the reflux continued for 3.5 h. Ethyl acetate (100 mL) and water (100mL) were added and the layers separated. The organic layer was washed with water, concentrated *in vacuo*, and mixed with water (300 mL) and potassium carbonate (6.0 g, 43 mmol). The mixture was refluxed 2 h and more potassium carbonate (3.0 g, 22 mmol) was added. After an additional hour of reflux, the solution was distilled, discarding the first 3 mL. Distillate was collected until no additional oil appeared. The distillate was mixed with water (100 mL) and heptane (100 mL), and separated. The organic layer was washed thrice with water and concentrated *in vacuo* to 2.0 g (25%) of yellow oil. ^{1}H NMR (300.0 MHz, $CDCl_3$): 7.93 (dd, J = 15.9, 7.8 Hz, 1H), 7.66 (dd, J = 7.3, 1.7 Hz, 1H), 6.98 (dd, J = 8.4, 2.7, 1H), 6.63 (s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 162.2 (d, J = 243.3 Hz), 156.3 (d, J = 12.6 Hz), 142.6 (d, J = 7.5 Hz), 118.3 (d, J = 4.1 Hz), 110.7 (d, J = 36.2 Hz), 70.0 . Anal. Calcd for $C_6H_4Cl_2FN$: C, 40.04; H, 2.24; Cl, 39.39. Found: C, 40.43; H, 2.13; Cl,.39.17.

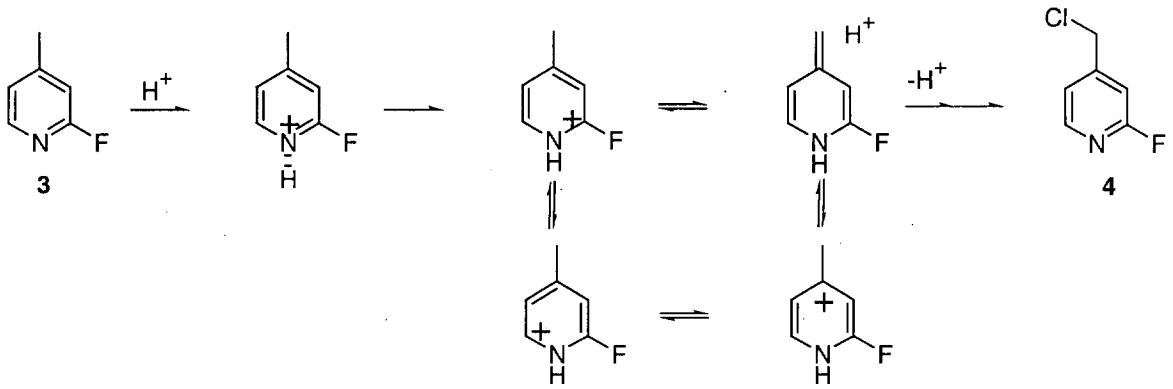
2-Chloro-6-(chloromethyl)pyridine (14a)[4] Prepared in ~96% yield from **14b**. An analytical sample was prepared by recrystallization from hexane (8 mL) to produce pale yellow crystals in 42% overall yield. Mp = 43-45 °C; ^{1}H NMR (300.0 MHz, $CDCl_3$): 7.69 (dd, J = 7.7, 7.7 Hz, 1H), 7.42 (d, J = 7.3 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 4.62 (s, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 157.4, 150.8, 139.6, 123.7, 121.2, 45.7. Anal. Calcd for $C_6H_5Cl_2N$: C, 44.48; H, 3.11; N, 8.64; Cl, 43.76. Found: C, 44.57; H, 3.02; N, 8.27; Cl, 43.46.

6-Chloro-2-pyridinemethanol (14b)[4] Isolated in ~62% yield over two steps from **14** as an orange oil. ^{1}H NMR (300.0 MHz, $CDCl_3$): 7.66 (dd, J = 7.8, 7.8 Hz, 1H), 7.27 (d, J = 14.1, 1H), 7.24 (d, J = 14.0 Hz, 1H), 4.75 (s, 2H), 3.60 (br s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 160.8, 150.6, 139.3, 122.7, 118.9, 64.2 . Anal. Calcd for C_6H_6ClNO: C, 50.19; H, 4.21; Cl, 24.69. Found: C, 49.92; H, 4.07; Cl, 24.55.

2-(Dichloromethyl)-6-chloropyridine (14c)[5] After **14** (5.78 g, 44.4 mmol) was chlorinated, hydrolyzed and worked up in the usual manner, the heptane wash of the aqueous product solution was concentrated *in vacuo* to 2.0 g. This was mixed with N-chlorosuccinimide (4.00 g, 30.0 mmol), benzoyl peroxide (0.40 g , 0.2 mmol), 1N HCl in acetic acid solution (0.25 mL, 0.25 mmol) and acetonitrile (15 mL) at reflux for 6.5 h. The mixture was worked up in the usual manner and resulting oil was submitted to the usual hydrolysis conditions. The solution was distilled until no additional organic components appeared in the distillate. The remaining aqueous heel was extracted twice with heptane, concentrated *in vacuo*, and the residue purified by column chromatography on silica gel (EtOAc:heptane 1:7) to produce 0.35 g (4% from **14**) of colorless oil. ^{1}H NMR (300.0 MHz, $CDCl_3$): 7.90-7.70 (m, 2H), 7.36 (dd, J = 7.5, 0.9 Hz, 1H), 6.66 (s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 158.5, 150.3, 140.3, 125.2, 119.7, 70.4 . Anal. Calcd for $C_6H_4Cl_3N$: C, 36.69; H, 2.05. Found: C, 36.86; H, 2.10.

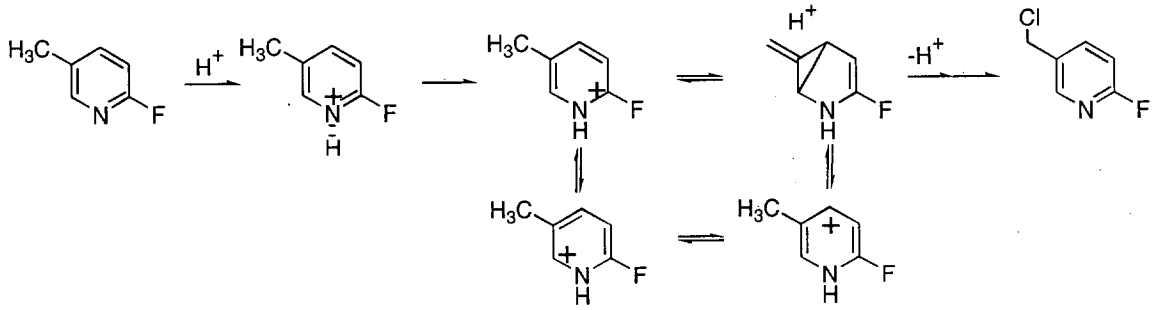
Expanded discussion of potential intermediates to benzylic chlorination of halo-picolines

One possibility to explain the increased rate of chlorination of **3** is a series of bond reorganizations initiated by protonation and terminated by proton loss via a hyperconjugative mechanism leading to a formal prototropic rearrangement:



Such a non-aromatic intermediate is likely either to be chlorinated directly by NCS with loss of a proton to re-aromatize the ring or to form a radical that would be stabilized by delocalization about the ring/sidechain until chlorination led to **4**. While the facts that **3** possesses a low pKa value due to the inductive effect of the 2-fluoro group and that acetic acid is a weak acid argue against a mechanism that requires initial *N* protonation, only a low concentration of protonated **3** might be needed if the subsequent steps are efficient. It could be possible to confirm such a pathway by comparing the chlorination rates of all of the 2-fluoropicoline isomers: the 3- and 5-methyl isomers **11** and **12** would not be able to convert to similar canonical intermediates upon protonation and their chlorination rates would be lower in comparison.

The chlorination rates of all of the isomeric 2-fluoropicolines as well as the chloro analog **14** displayed similar rates whether compared in the presence of additional acid (fast) or of an acid scavenger (slow). Only the chlorination rate of 2-picoline displayed no significant difference between the two sets of conditions. In light of the sum of these observations, the prototropic rearrangement explanation seems unlikely. However, a related possibility is interesting to consider. If a diradical trimethylenemethane moiety (drawn here as the closed methylenecyclopropyl resonance structures) is allowed, a similar series of bond reorganizations would lead to the chlorinated products for **11** and **12**.



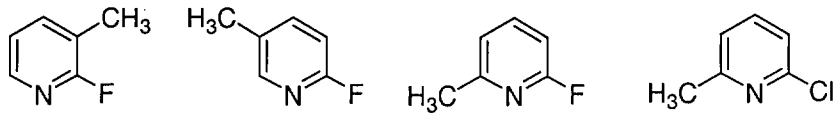
Trimethylenemethane and its equivalents have been extensively examined, proposed as intermediates in a variety of reactions and found use in synthetic chemistry, principally in cycloadditions.[6] It's potential as an intermediary arising from hyperconjugation leading to chlorination is conceivable although there are no examples of trimethylenemethane systems condensed within larger ring systems. While such a constraint is likely to further increase the energy of the intermediate, offsetting this are a large number of equivalent resonance structures possible by calling upon the diradical or dipolar analogs. In particular, dipolar structures can interact profitably with the nitrogen and fluorine atoms via inductive and resonance effects.

It is unlikely different mechanisms for prototropic rearrangement would proceed with similar rates as Figures 1 and 2 indicate, unless the offsetting effects of the inherent strain of the trimethylenemethane system and the newly possible canonical structures cancel each other. This mechanism also does not account for the results of 2-picoline chlorination. While the possibility of coincidence cannot be eliminated, these results point toward other factor(s) universal to the substrates and led us to assume the increase in chlorination rate is due to the acid reaction with NCS.

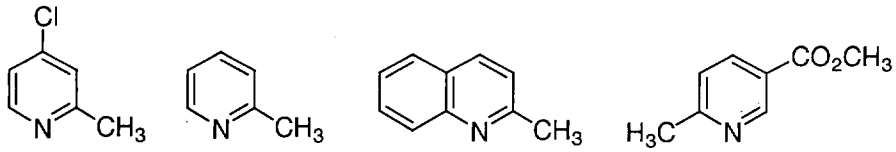
It's worthwhile to discuss the potential for interaction of the fluorine atom within the hypothesized intermediates. Perhaps an explanation of why such a weak acid as acetic acid may still be able to effectively protonate **3** for the purposes of chlorination is the influence of the fluorine atom. It would be particularly satisfying to hypothesize protonation stabilized by hydrogen bonding to the adjacent fluorine to produce a bridged proton system but such structures are unlikely since 1) 'bent' hydrogen bonds to halogens are weak;[7] 2) four-membered ring halonium ions are not known;[8] 3) and in spite of the high electronegativity of the fluorine atom, they rarely forms hydrogen bonds.[9] It's less clear if a fluoronium ion can be excluded. A double-bonded fluoronium intermediate would add yet one more canonical structure to the variety that may form, would stabilize the putative cation by resonance,[10] and would begin to explain the curious basicity we are assuming to explain the enhanced chlorination rate. Inductive effects of aromatic halogens are generally assumed to outweigh those of resonance effects, but it may be enough to ameliorate the inductive effect to permit the prototropic rearrangement to proceed efficiently. While such halonium intermediates are well established for other halogens, fluoronium ions are at best rare.[11,12]

The chlorination rate increase from the addition of acid to NCS chlorinations of picolines is not general for the examples we examined. The presence of an ortho-halo atom was

necessary for an useful reaction. Reversing the position of the methyl and halo groups as in 4-chloro-2-methylpyridine (**15**) produced little or no chlorination after 5 h in the presence of 0.21 equivalents of acetic acid. 2-Picoline (**16**) produced 2-(chloromethyl)pyridine slowly whether acid was present or not, (attempts to use these conditions to chlorinate 3- or 4-picoline led to complex mixtures that were not analyzed). 2-Methylquinoline (**17**) was polychlorinated[13] very rapidly whether acid was present or not, negating the value of the procedure (the data for these last two examples appear in the following tables). Finally, methyl 6-methylnicotinate (**18**) also produced a complex mixture of products under all conditions. Beyond the limited category of ortho-halo picolines, this procedure is not useful.



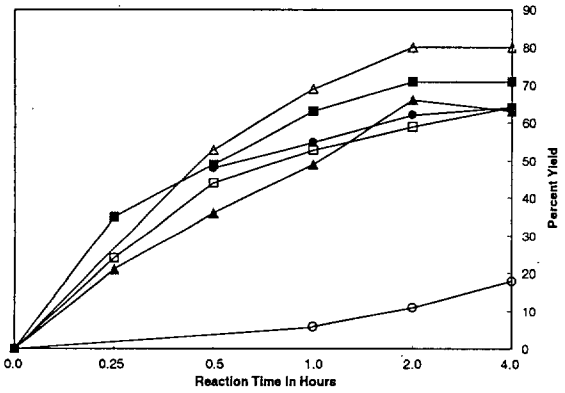
11 **12** **13** **14**



15 **16** **17** **18**

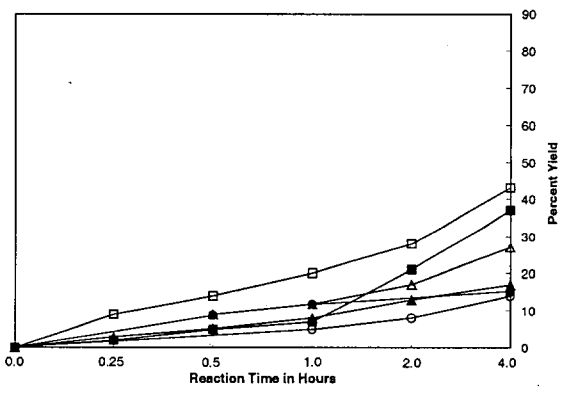
The effect of acid upon factors other than the substrate was considered. Some interaction of acid with the solvent acetonitrile is certain, although whether this would influence the chlorination is less so. When the chlorination rate of **3** was compared under acid/acid scavenged conditions in carbon tetrachloride, the order of reactivity reversed: in the presence of acid, only a 5% yield of **4** occurred after 3 h while in the presence of propylene oxide, the yield was 33%. Both of these rates are still lower than that in acetonitrile.

Figure 1. Monochloride yield vs time



for acidified medium.

Figure 2. Monochloride yield vs time



for acid-scavenged medium.

Symbol key: ■ (**4**); ▲ (**11a**); □ (**12a**); ● (**13a**); △ (**14a**), ○ (**16a**). Yield values for mono- and dichlorides are tabulated in Tables 1 and 2.

Table 1. NCS Chlorination Under Acid Catalysis Conditions.[a]

		monochloride / dichloride % yields at T = X h.				
Substrate	Product	0.25 h	0.5 h	1.0 h	2.0 h	4.0 h
3	**3a**	35/2	49/4	63/8	71/15	71/16
11	**11a**[b]	21/<1	36/1	49/2	66/5	63/9
12	**12a**[b]	24/<1	44/2	53/3	59/4	64/5
13	**13a**	<1/<1	48/3	55/4	62/11	64/15
14	**14a**	<1/<1	53/4	69/8	77/15	80/16
16	**16a**	<1/<1	<1/<1	6/<1	11/<1	18/<1
17	**17a**	53/9	45/44	43/46	NS[c]	43/49

[a] Reaction conditions: 1.8 M substrate in acetonitrile, 1.5 equivalents of NCS and 0.02 equivalents of benzoyl peroxide, 0.10 equivalents of 1.0 M hydrochloric acid in acetic acid. [b] Dichloride of substrate could not be prepared; yield of dichloride estimated based on its area ratio to chloride and then corrected for the LC area response ratio average measured for **14a/14c**. [c] Not sampled.

Table 2. NCS Chlorination Under Acid Scavenging Conditions.[a]

		monochloride / dichloride % yields at T = X h.				
Substrate	Product	0.25 h	0.5 h	1.0 h	2.0 h	4.0 h
3	**3a**	2/<1	5/<1	7/<1	21/<1	37/2
11	**11a**[b]	3/<1	5/<1	8/<1	13/<1	17/<1
12	**12a**[b]	9/<1	14/<1	20/<1	28/<1	43/2
13	**13a**	NS[c]	9/<1	12/<1	NS	15/<1
14	**14a**	NS	9/<1	12/<1	17/<1	27/<1
16	**16a**	NS	NS	5/<1	8/<1	14/<1
17	**17a**	22/1	51/7	60/22	NS	50/45

[a] Reaction conditions: 1.8 M substrate in acetonitrile, 1.5 equivalents of NCS and 0.02 equivalents of benzoyl peroxide, and 0.10 equivalents of propylene oxide as acid scavanger. [b] Dichloride of substrate could not be prepared; yield of dichloride estimated based on its area ratio to chloride and then corrected for the LC area response ratio average measured for **14a/14c**. [c] NS: not sampled.

References

(1) Preparation of **5** and **8** and ^{1}H NMR spectrum of **8**: Earl, R.A., Zaczek, R.; Teleha, C.A.; Fisher, B.N.; Maciag, C.M.; Marynowski, M.E.; Logue, A.R.; Tam, S.W.; Tinker, W.J.; Huang, S.M.; Chorvat, R.J. *J. Med. Chem.* **1998**, *41*, 4615-4622.

(2) Preparation and ^{1}H NMR spectrum: Atsuyuki, A.; Ono, T.; Uchida, T.; Ohtaki, Y.; Fukaya, C.; Watanabe, M.; Yokoyama, K. *Chem. Pharm. Bull.* **1990**, *38*, 2446-2458.

(3) Preparation: Carlson, L.A.; Hedbom, C.; Helstrand, E.; Misiorny, A.; Sjoberg, B.; Stjernstrom, N.E.; Westin, G. *Acta. Pharm. Suecica* **1972**, *9*, 411-418.

(4) Preparation and ^{1}H and ^{13}C NMR spectra: (a) Barnes, J.H.; Hartley, F.R.; Jones, C.E.L. *Tetrahedron* **1982**, *38*, 3277-3280. (b) Lee, K.C.; Chi, D.Y. *J. Org. Chem.* **1999**, *64*, 8576-8581.

(5) Preparation and ^{1}H and ^{13}C NMR spectra: Orvik, J.A. *J. Org. Chem.* **1994**, *59*, 12-17.

(6) (a) Allan, A.K.; Carroll, G.L.; Little, R.D. *Eur. J. Org. Chem.* **1998**, 1-12 and references therein. (b) Trost, B.M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1-20 and references therein. (c) Borden, W.T. Diradicals. In *Diradicals as Reactive Intermediates, Vol. 2* , pp. 198-204; John Wiley & Sons: London, 1981 and references therein.

(7) Modena, G.; Scorrano, G. Directing, activating and deactivating effects. In *The chemistry of the carbon-halogen bond, Part 1*; Patai, S., Ed.; p 267-268; John Wiley & Sons: London, 1973;

(8) March, J *Advanced Organic Chemistry*, 4th Ed., John Wiley and Sons, New York, 1992, pp. 308-312.

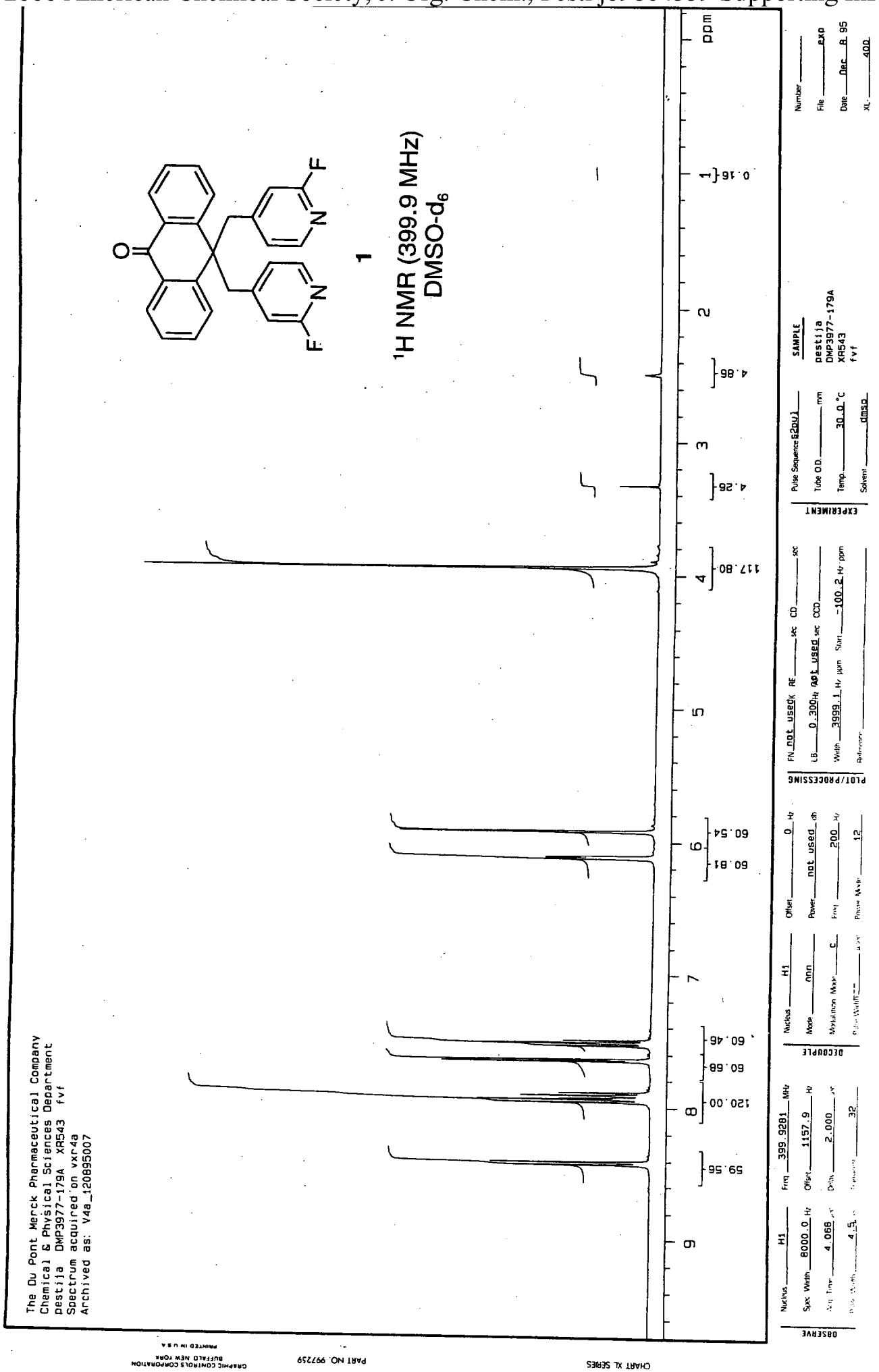
(9) Dunitz, J.D.; Taylor, R. *Chem. Eur. J.* **1997**, *3*, 89-98.

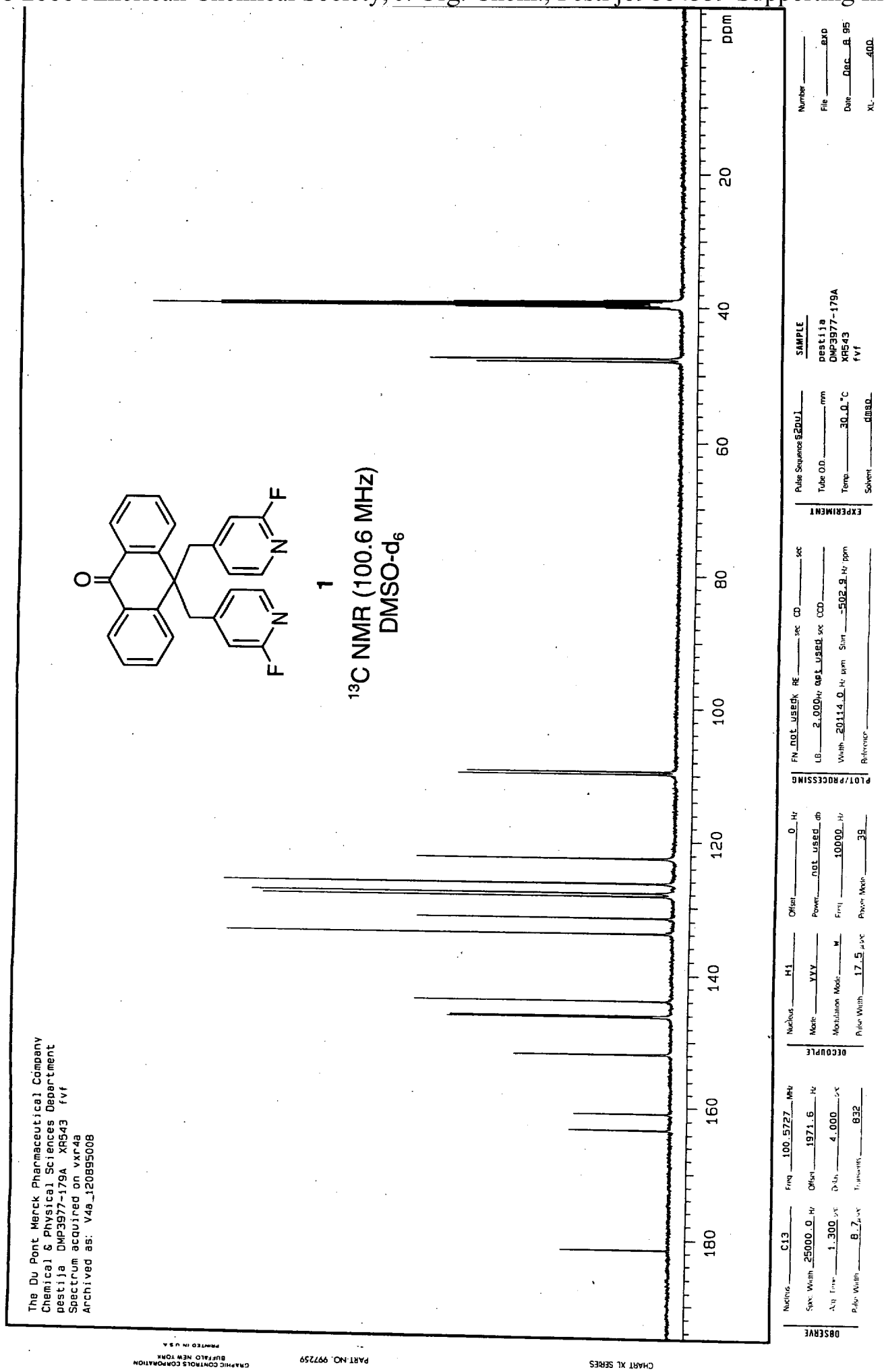
(10) Fisher, T.H.; Meierhoefer, A.W. *J. Org. Chem.* **1978**, *43*, 224-228.

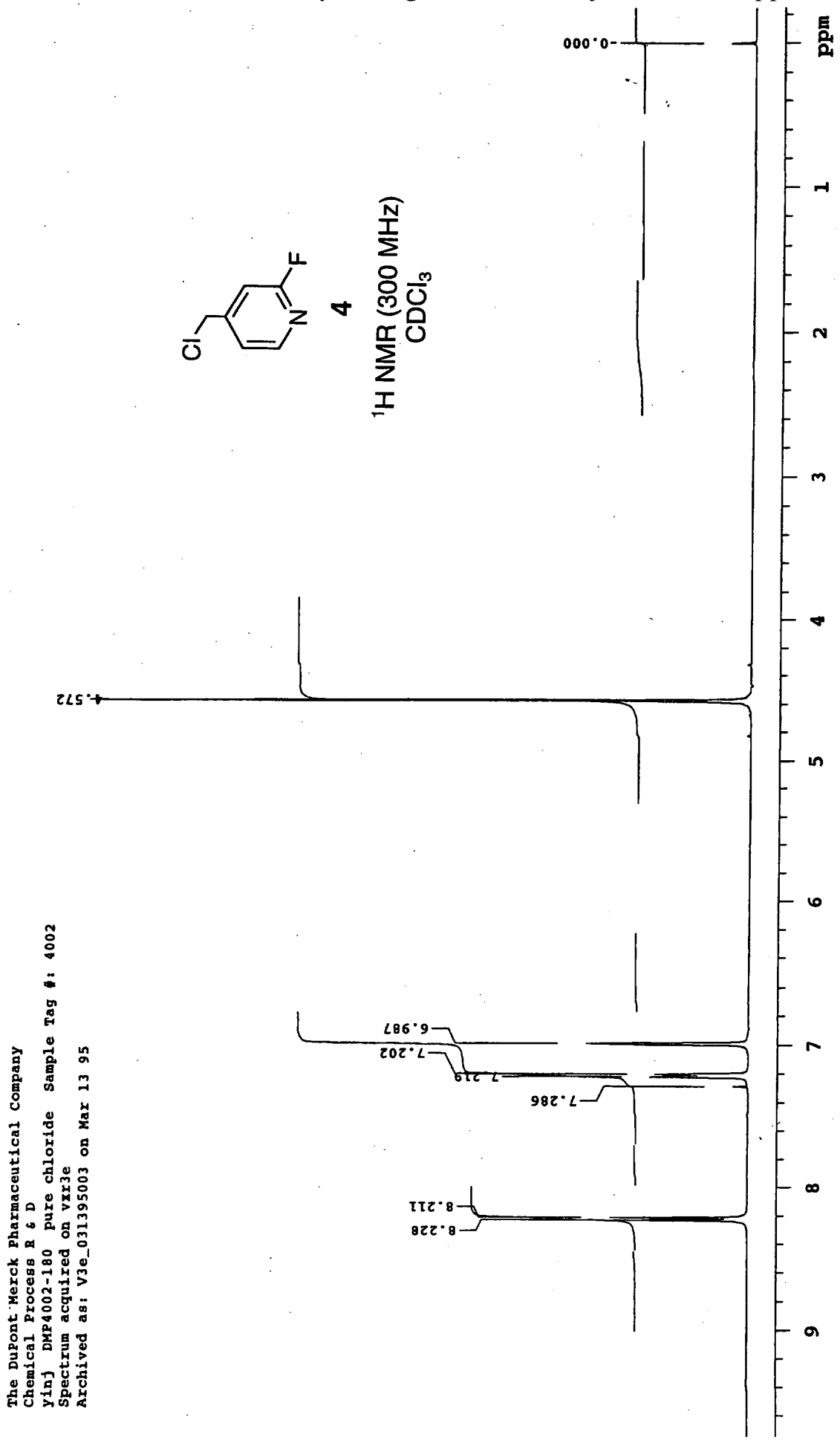
(11) Olah, G.A. *Halonium Ions*; John Wiley & Sons: New York, 1975, pp. 108-111, 125-133.

(12) Modena, G.; Scorrano, G. Directing, activating and deactivating effects. In *The chemistry of the carbon-halogen bond, Part 1*; Patai, S., Ed.; pp. 301-406; John Wiley & Sons: London, 1973;

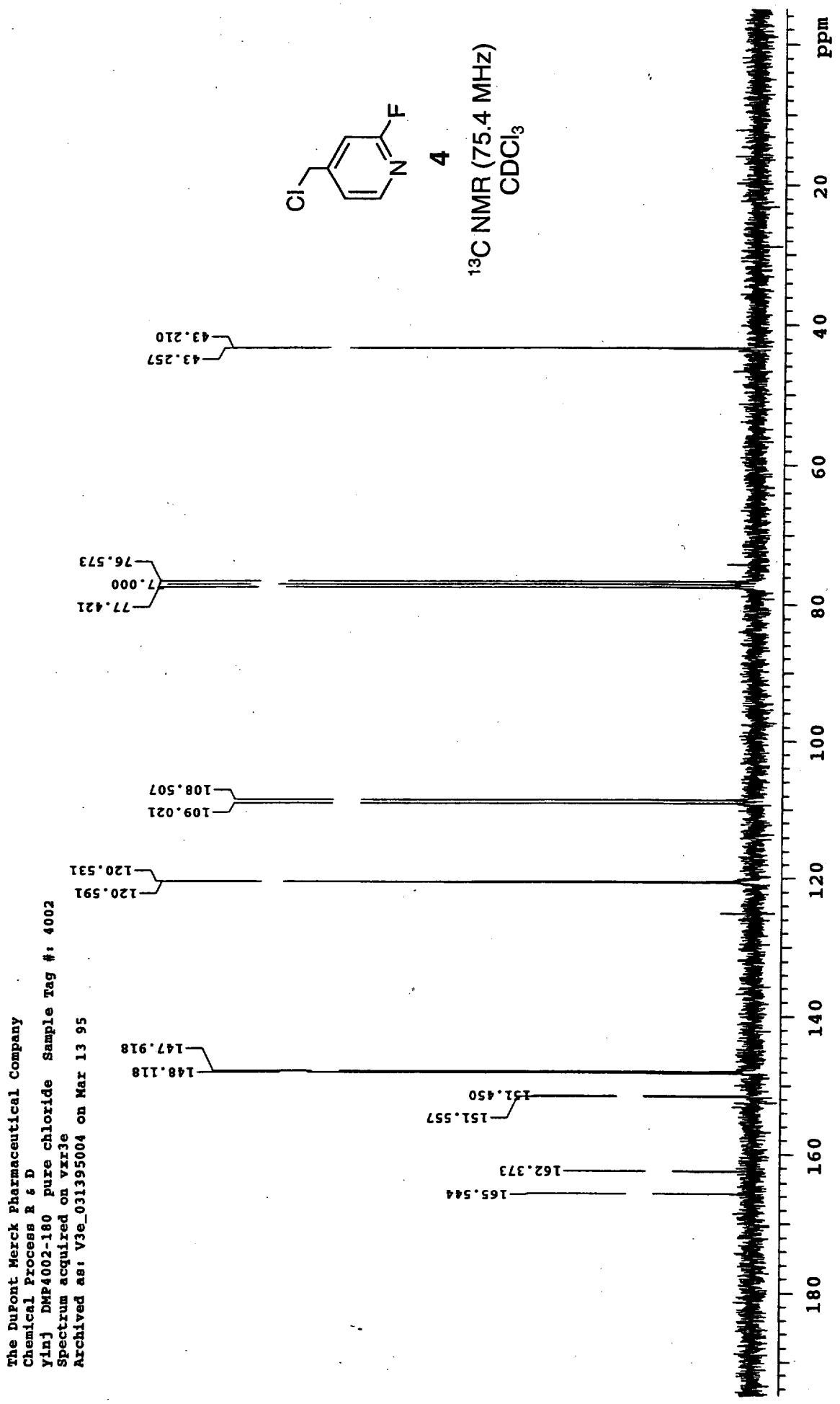
(13) Preparation and ^{1}H NMR spectrum of 2-(dichloromethyl)quinoline; the monochloride is commercially available: Jeromin, G.E.; Orth, W.; Rapp, B.; Weiss, W. *Chem. Ber.* **1987**, *120*, 649-651.

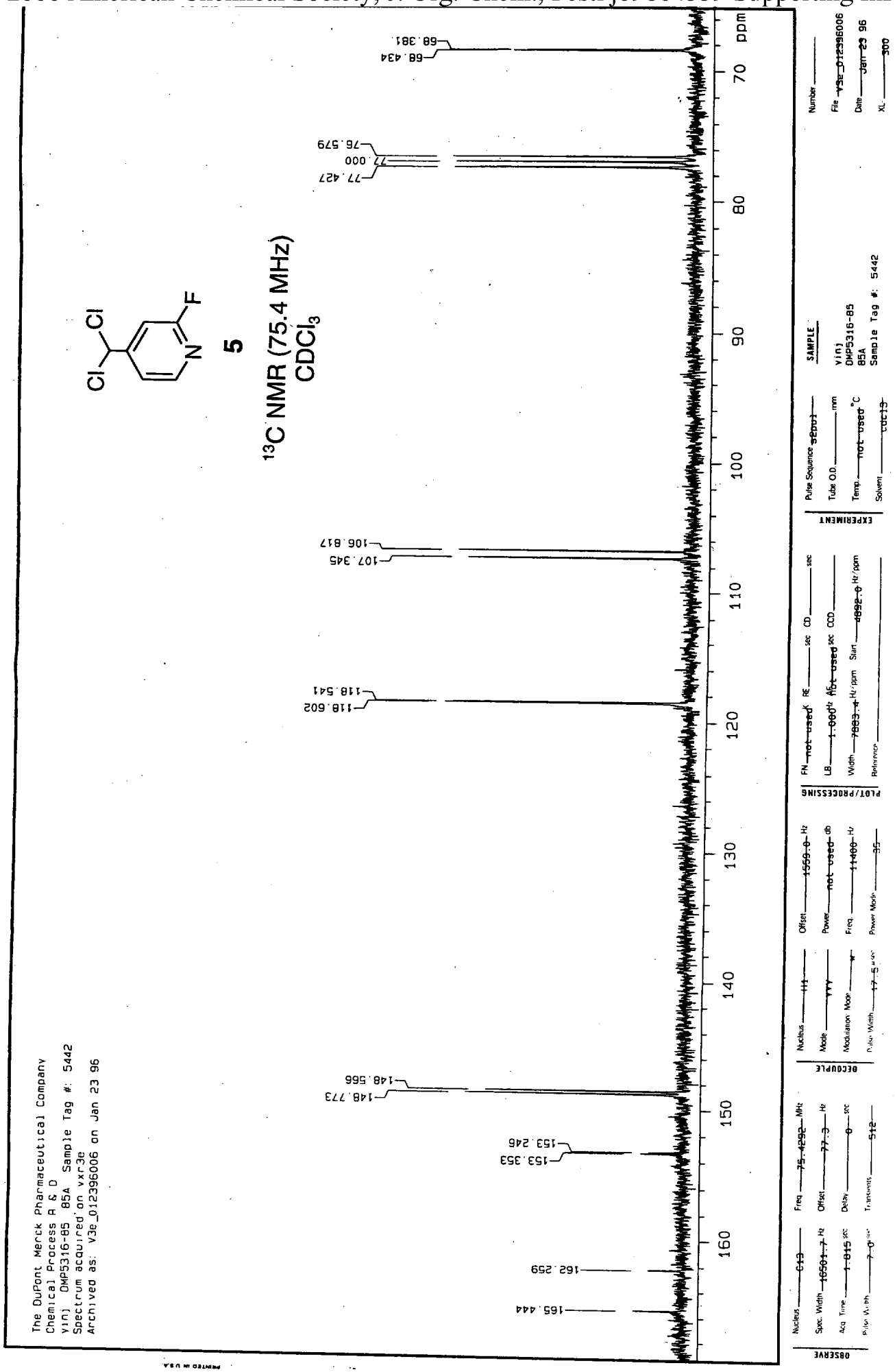


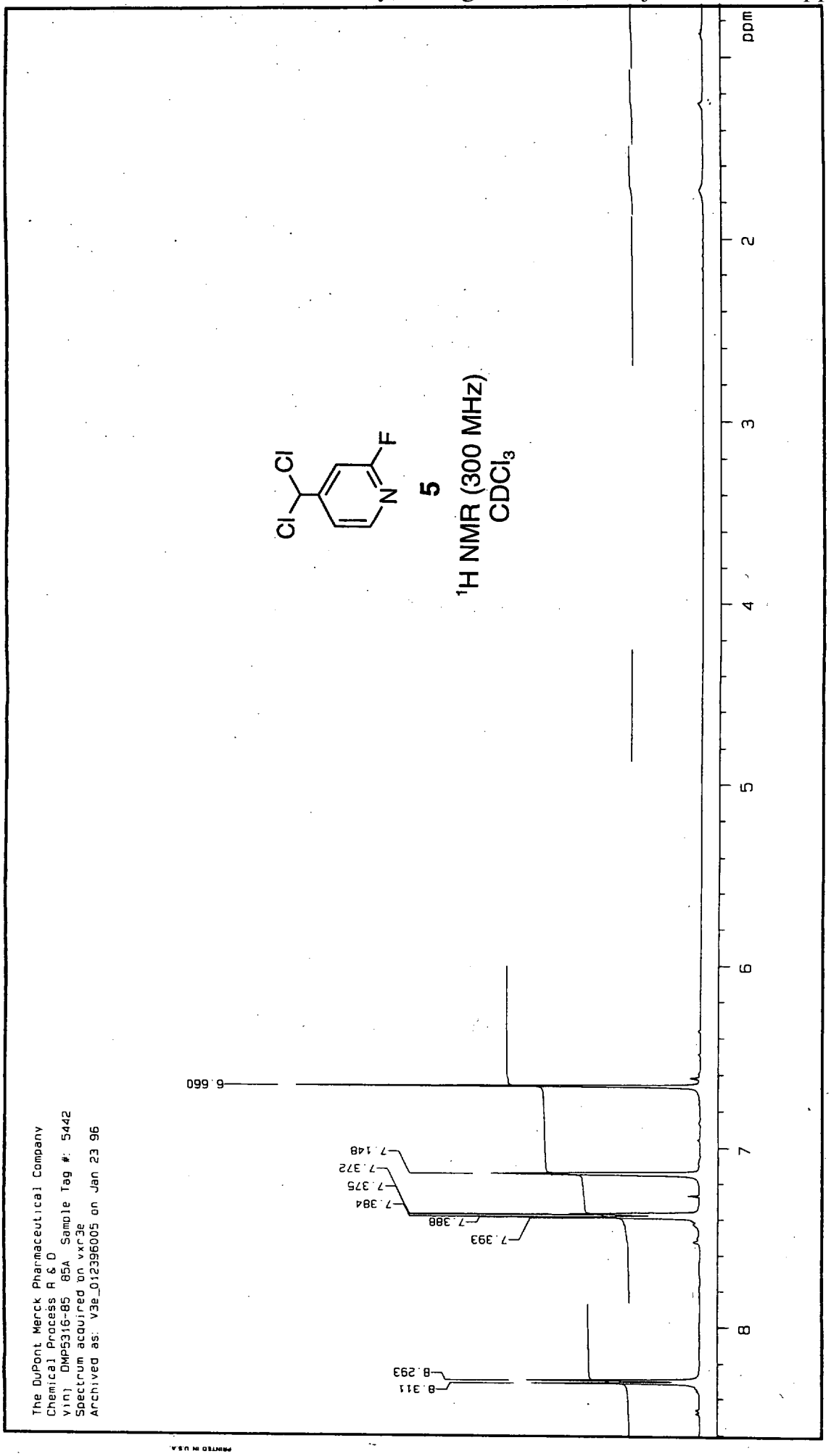


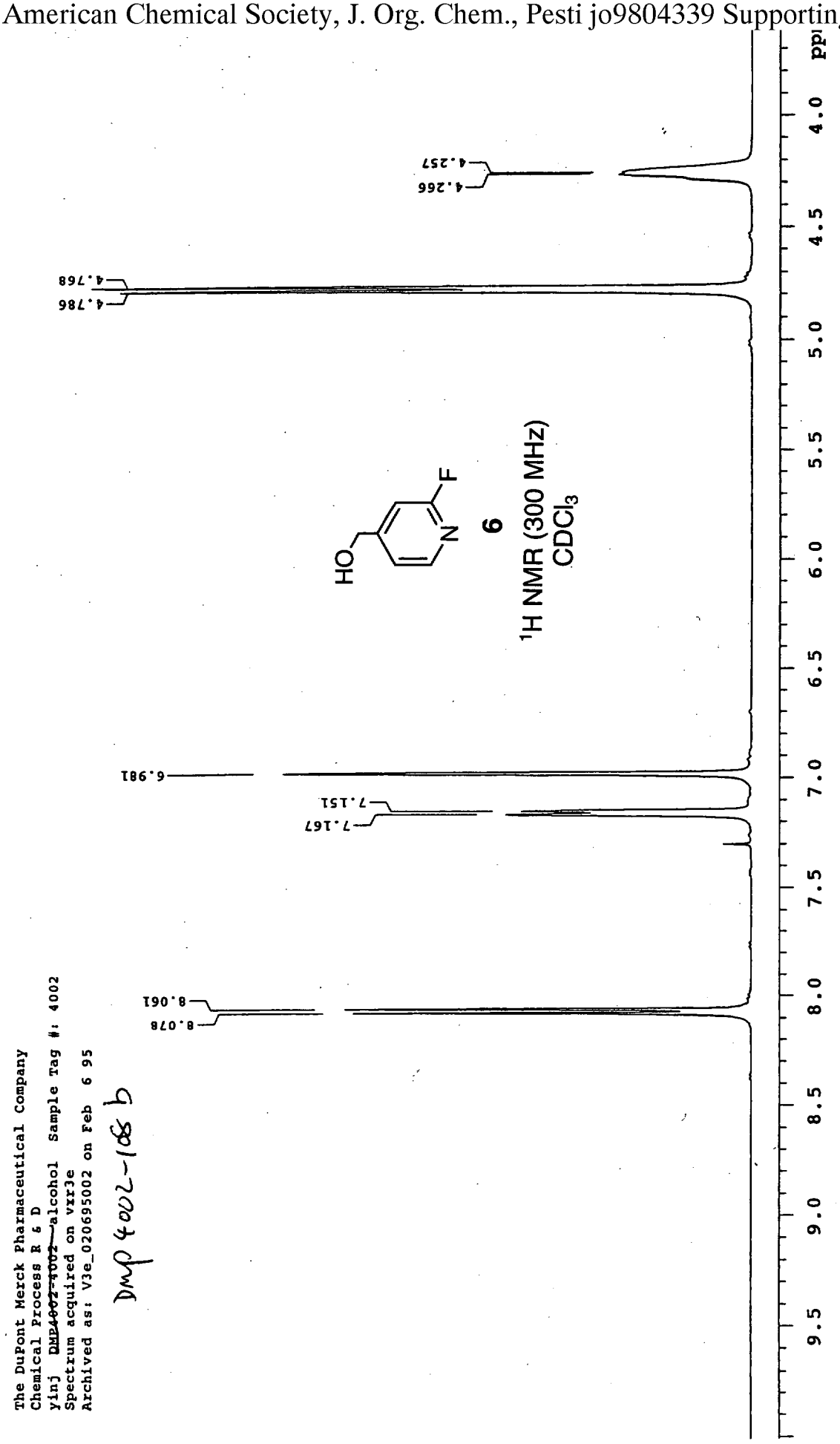


The DuPont Merck Pharmaceutical Company
Chemical Process R & D
yinj DMP4002-180 pure chloride Sample Tag #: 4002
Spectrum acquired on vxr3e
Archived as: V3e_01395003 on Mar 13 95


4
^{13}C NMR (75.4 MHz)
$CDCl_3$
Cl
F
N
ppm
20
40
60
80
100
120
140
160
180
43.210
43.257
76.573
77.000
77.421
108.507
109.021
120.531
120.591
147.918
148.118
151.450
151.557
162.373
165.544
The DuPont Merck Pharmaceutical Company
Chemical Process R & D
ylmj DMP4002-180 pure chloride Sample Tag #: 4002
Spectrum acquired on vxr3e
Archived as: V3e_031395004 on Mar 13 95

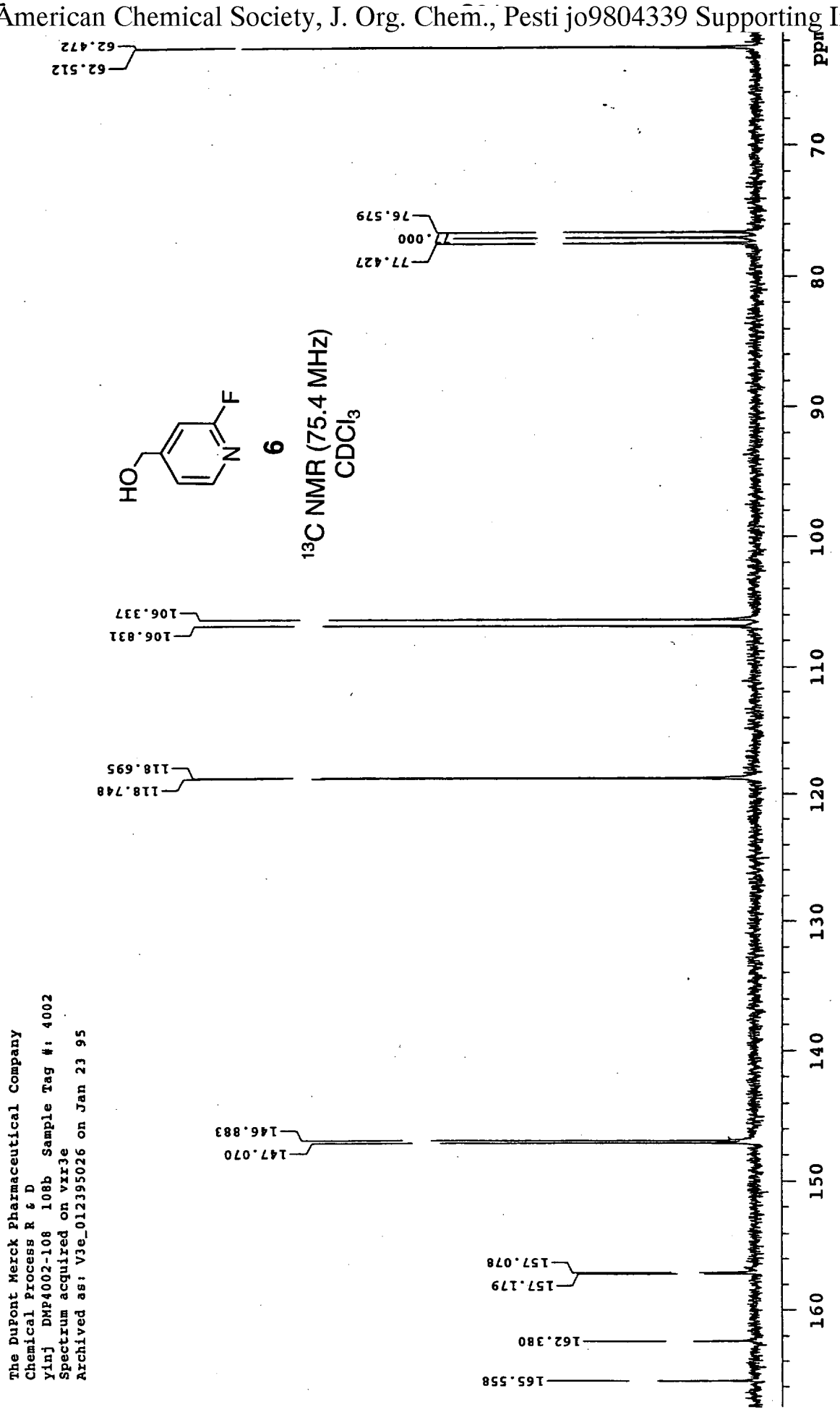

5
^{13}C NMR (75.4 MHz)
$CDCl_3$
68.381
68.434
76.579
77.000
77.427
106.817
107.345
118.541
118.602
148.566
148.773
153.246
153.353
162.259
165.444
ppm
The DuPont Merck Pharmaceutical Company
Chemical Process R & D
vinj DMP5316-85 85A Sample Tag #: 5442
Spectrum acquired on vxr3e
Archived as: V3e_012396006 on Jan 23 96
OBSERVE
DECOUPLE
PLOT/PROCESSING
EXPERIMENT
SAMPLE
Pulse Sequence
Tube O.D.
Temp. not used °C
Solvent CDCl3
vinj
DMP5316-85
85A
Sample Tag #: 5442
Number
File V3e_012396006
Date Jan 23 96
XL 300
CHART XL SERIES
PART NO. 997259



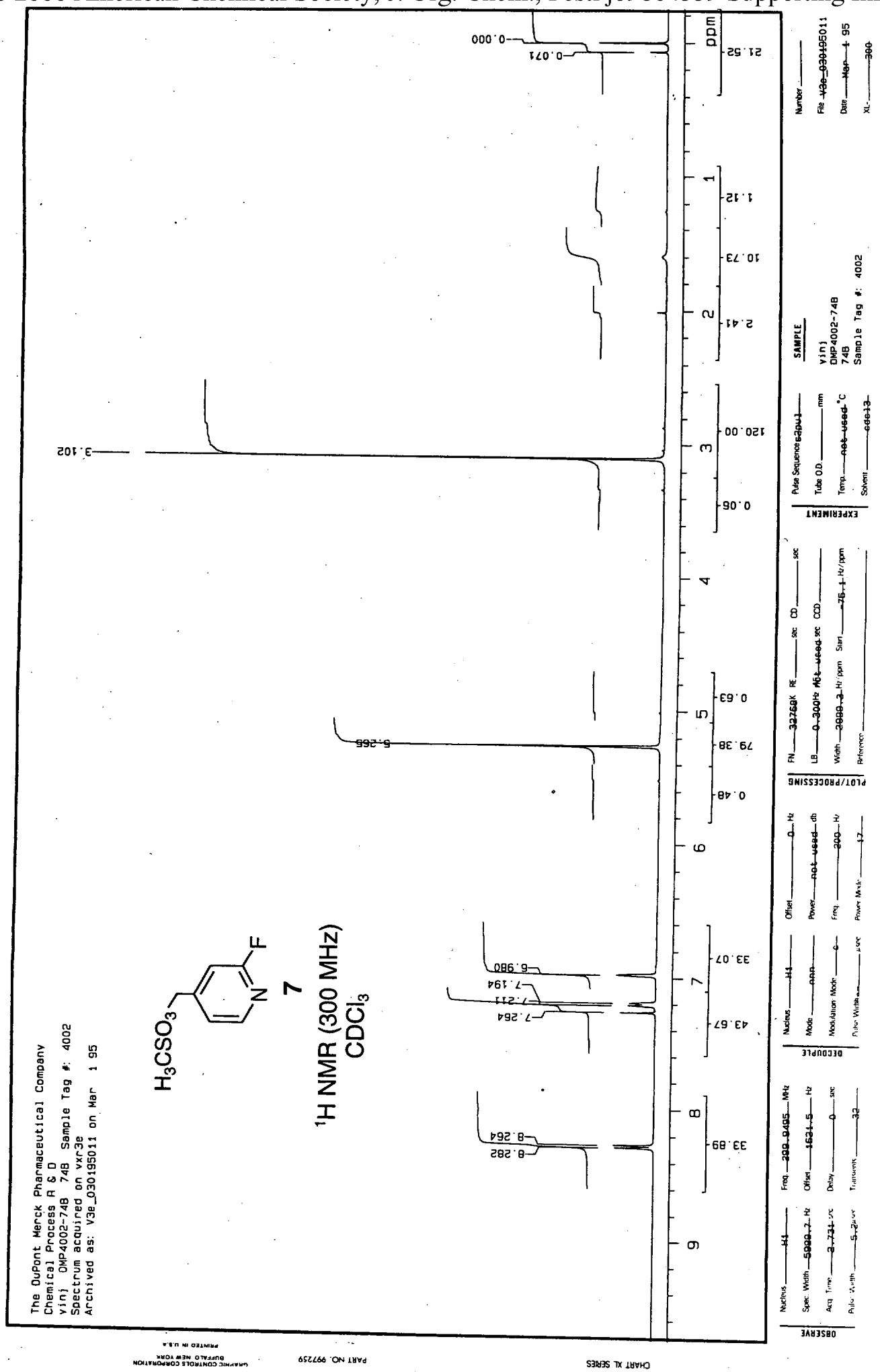


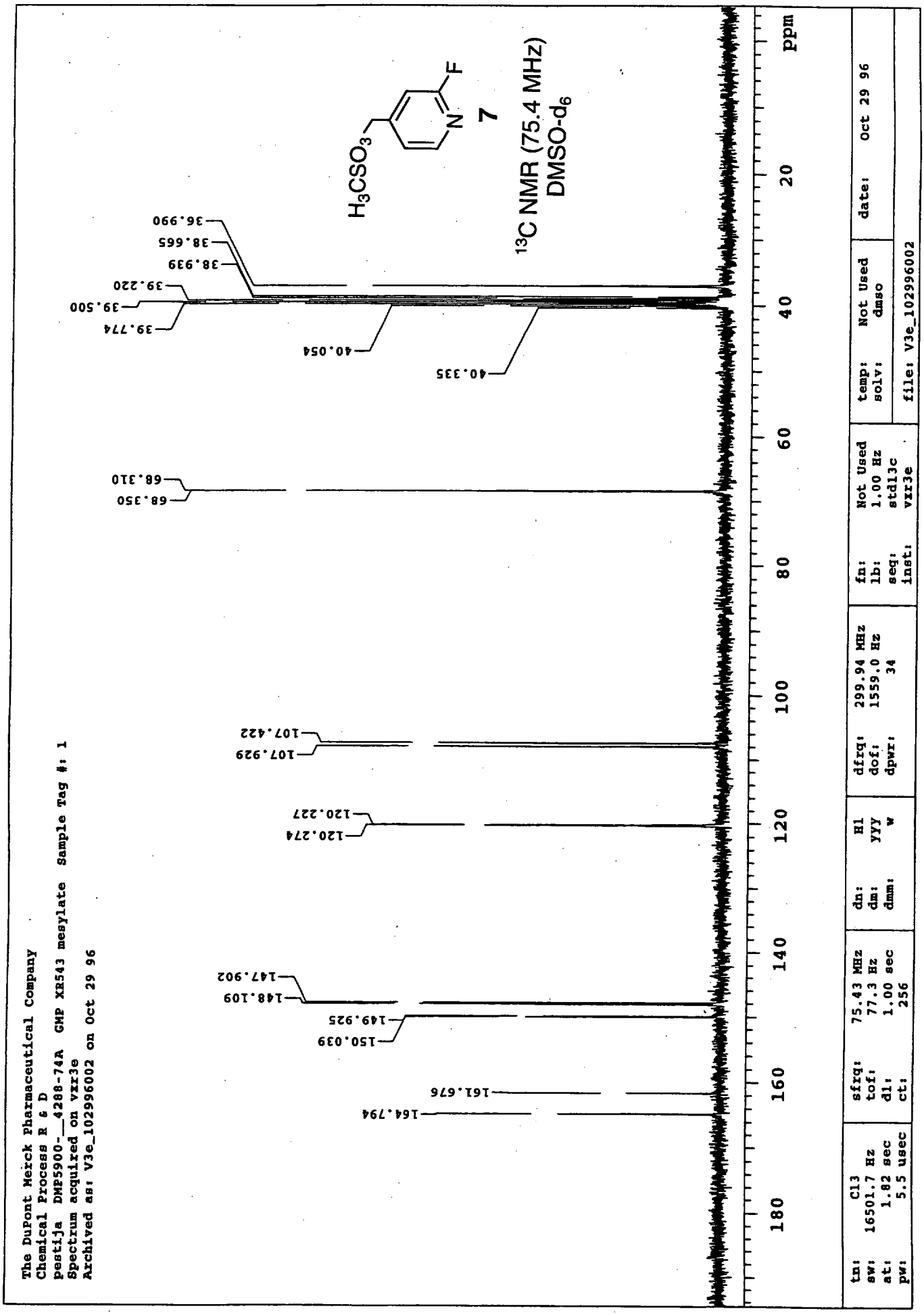
The DuPont Merck Pharmaceutical Company
Chemical Process R & D
yinj DMP4002-4002—alcohol Sample Tag #: 4002
Spectrum acquired on vxr3e
Archived as: V3e_020695002 on Feb 6 95

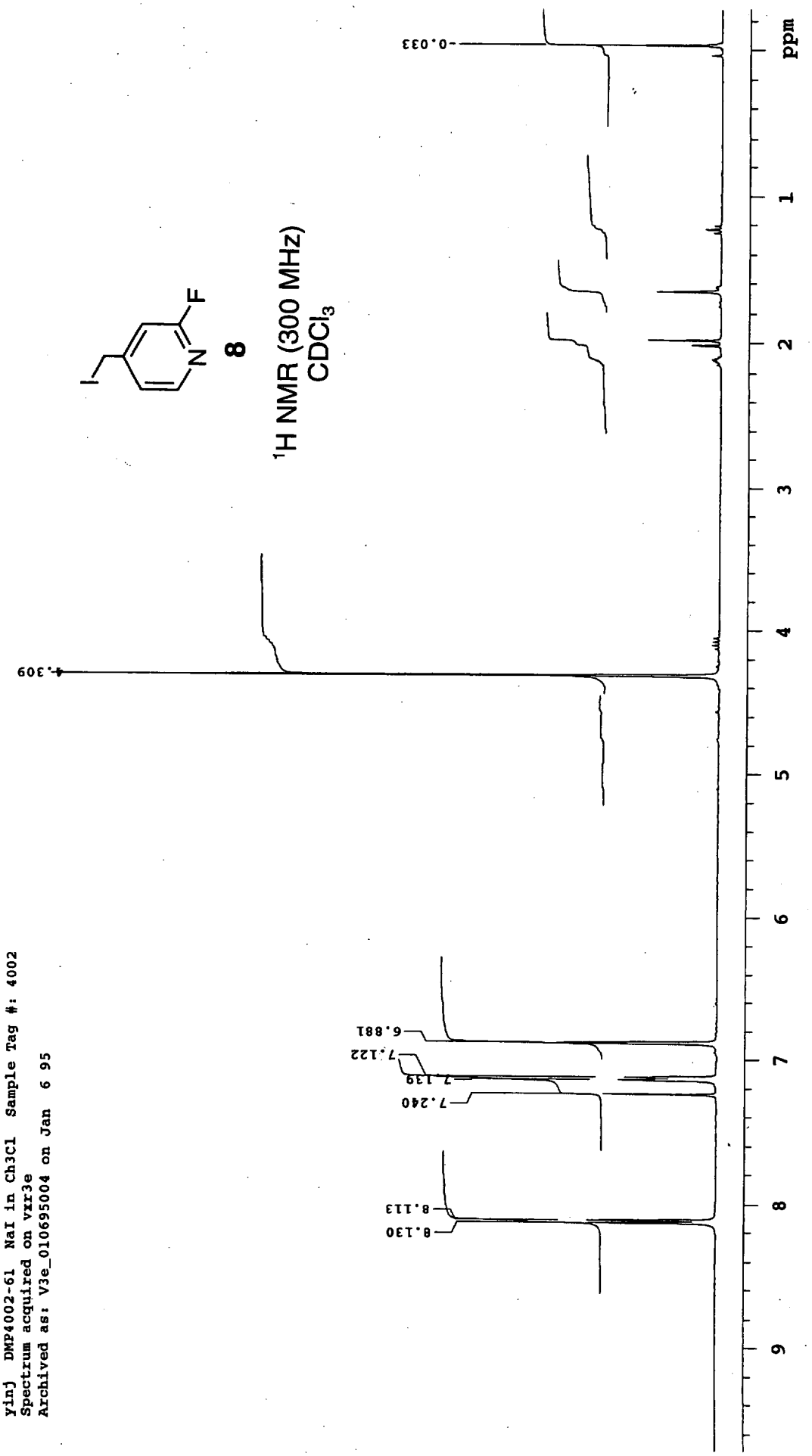
DMP 4002-108 b

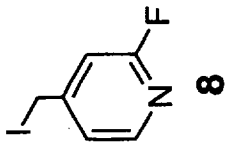


The DuPont Merck Pharmaceutical Company
Chemical Process R & D
yinj DMP4002-108 108b Sample Tag #: 4002
Spectrum acquired on vxr3e
Archived as: V3e_012395026 on Jan 23 95



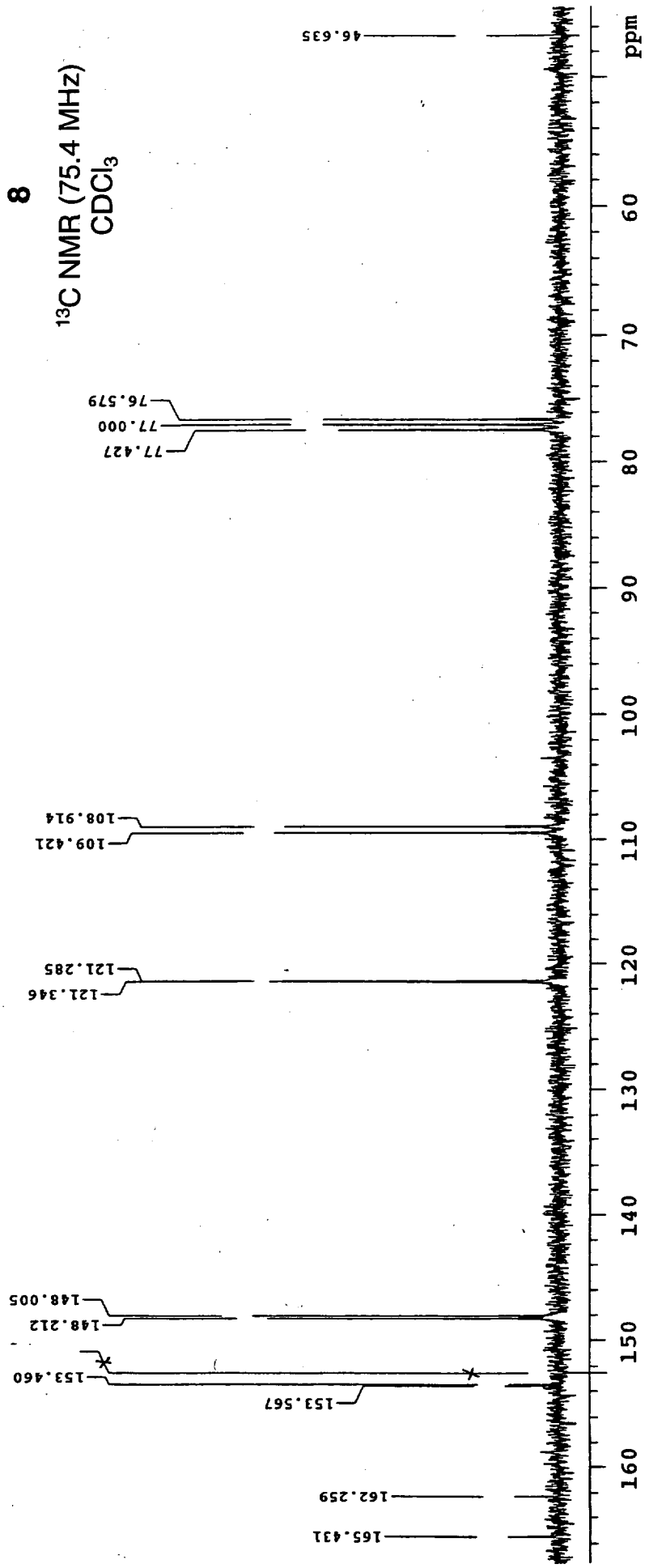




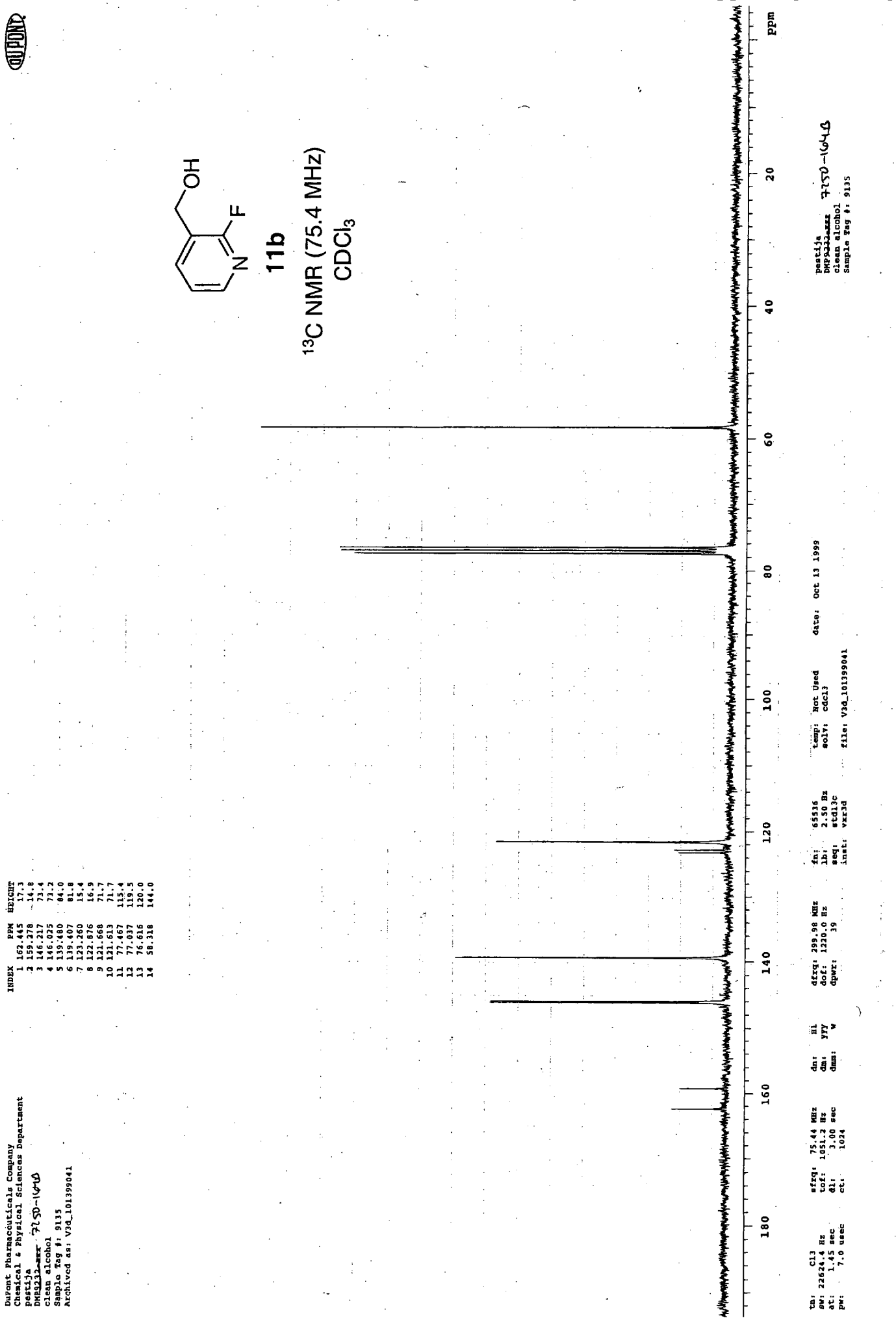


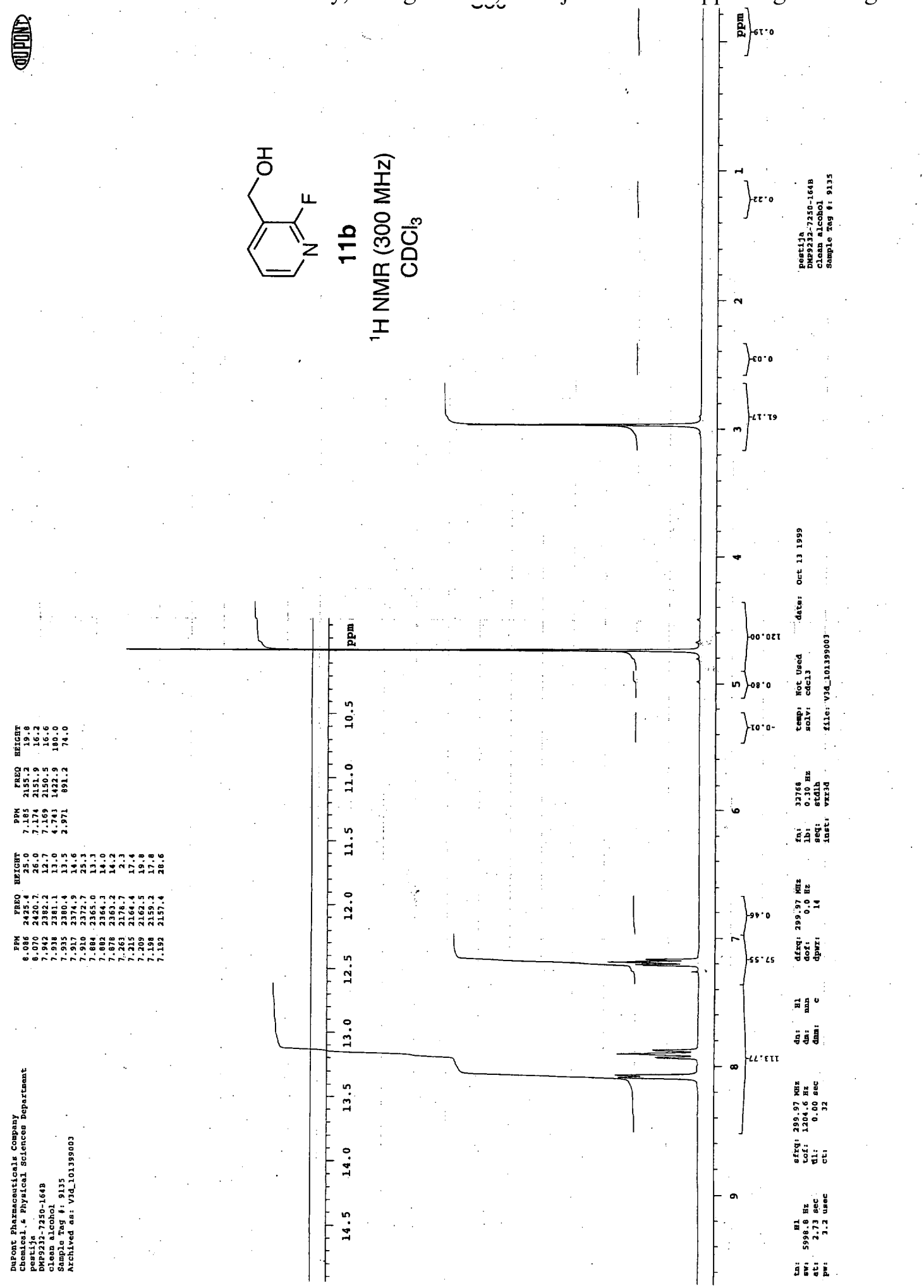
8

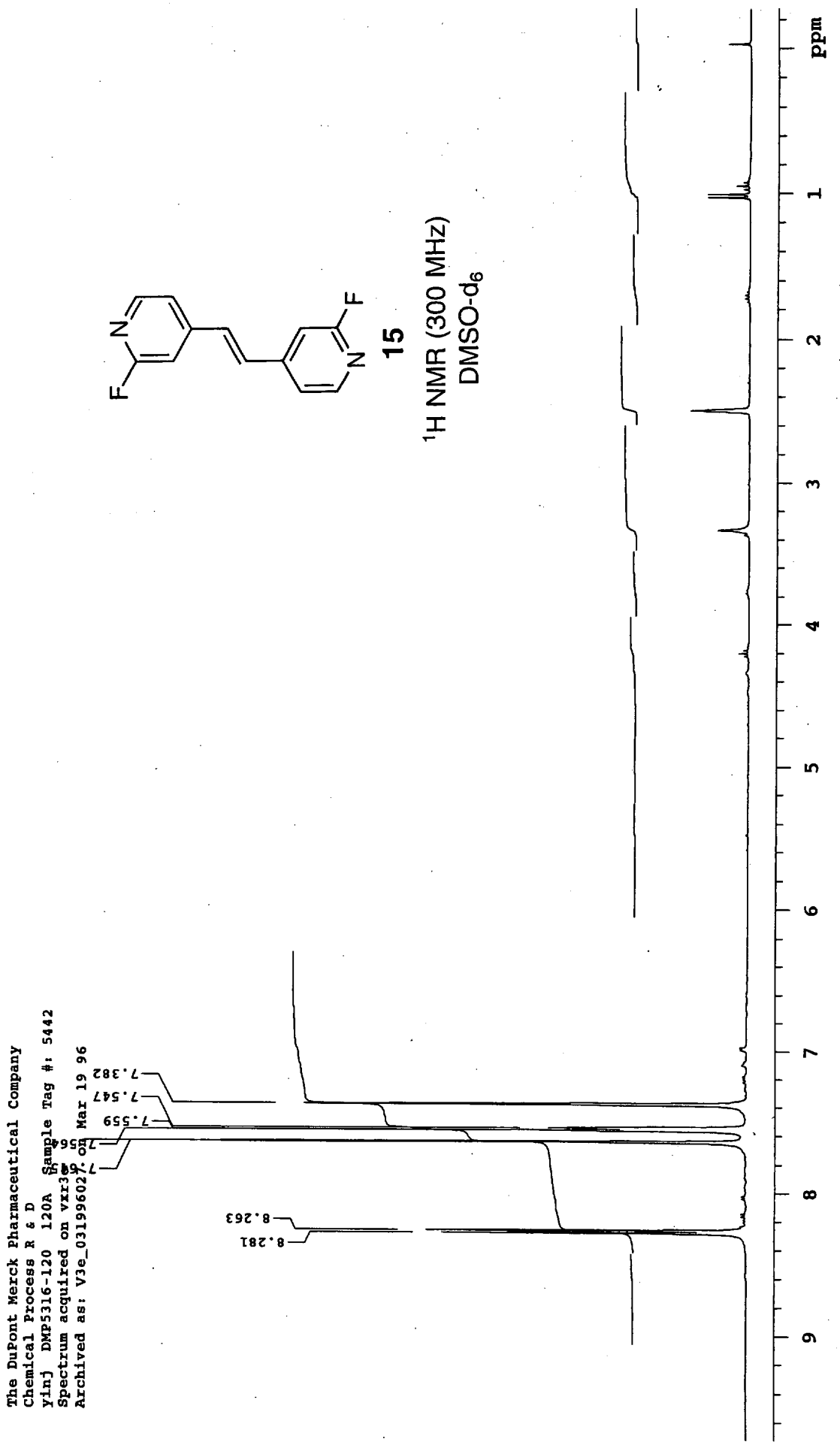
^{13}C NMR (75.4 MHz)
$CDCl_3$

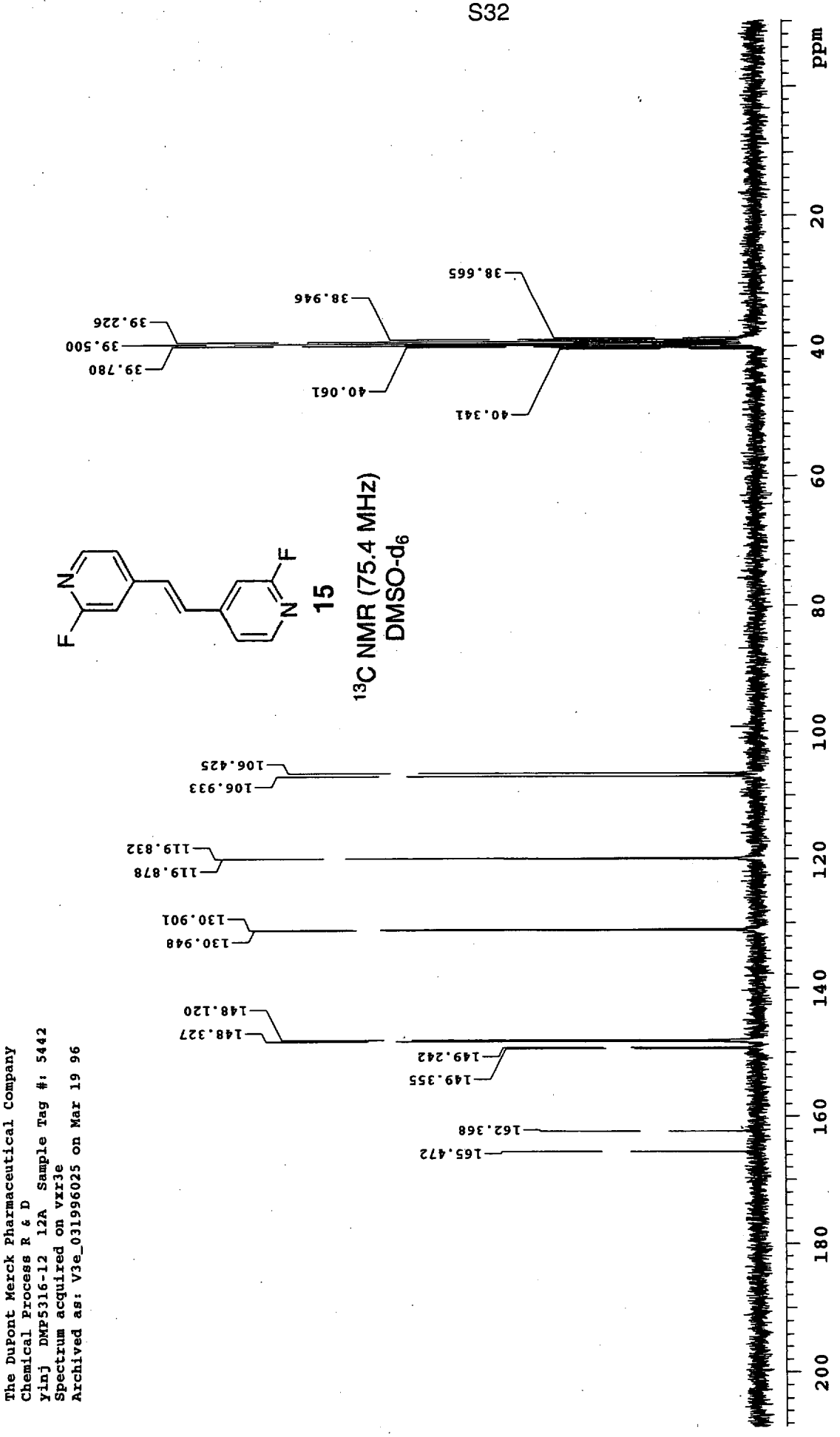


The DuPont Merck Pharmaceutical Company
Chemical Process R & D
yinj DMP4002-110 110 Sample Tag #: 4001
Spectrum acquired on vxr3e
Archived as: V3e_012795028 on Jan 27 95








ppm
20
40
60
80
100
120
140
160
180
200
38.665
38.946
39.226
39.500
39.780
40.061
40.341
106.425
106.933
119.832
119.878
130.901
130.948
148.120
148.327
149.242
149.355
162.368
165.472
15
^{13}C NMR (75.4 MHz)
DMSO-d_6
N
F
N
F
The DuPont Merck Pharmaceutical Company
Chemical Process R & D
yinj DMP5316-12 12A Sample Tag #: 5442
Spectrum acquired on vxr3e
Archived as: V3e_031996025 on Mar 19 96