Spectral Characterization of 2,4-Dimethoxy-3-methylphenethylamine, and Comparison to 2,5-Dimethoxy-4-methylphenethylamine ("2C-D")

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ABSTRACT: Synthesis and analytical data for 2,4-dimethoxy-3-methylphenethylamine (**2**) and its hydrochloride salt (**3**) are described. **2** was synthesized from 2,4-dimethoxy-3-methylbenzaldehyde via *trans*-2,4-dimethoxy-3-methyl-β-nitrostyrene (**1**). The compounds were characterized by ^{1}H NMR, ^{13}C NMR, GC/MS, and FTIR. The data was compared to 2,5-dimethoxy-4-methylphenethylamine (2C-D).

KEYWORDS: Designer Drugs, Dimethoxyphenethylamines, Synthesis, Isomescaline, 2C-D, Desoxy, TIM, Forensic Chemistry

Introduction

A large number of phenethylamines derivatives are known, many of which have been reported to have CNS-stimulant and/or psychoactive properties.[1] As a result, many phenethylamines compounds are listed as controlled substances. Notably, for each of these controlled substances are various possible isomers differing only in the positioning of the phenyl substituents. These positional isomers and analogues are (with few exceptions) not formally controlled; however, they may be prosecuted under the Analogue Statute of the Controlled Substances Act.

Examples of positional isomers that have circulated in the chemical underground are 2,5-dimethoxy-4-methylphenethylamine HCl (also known as "2C-D") and 3,5-dimethoxy-4-methylphenethylamine HCl (also known as "DESOXY").[1] Recently, an exhibit containing 2C-D was received at this laboratory. Interestingly, the ^{1}H NMR spectrum of 2C-D displays two singlets in the aromatic region that could potentially be confused for a doublet, albeit with a suspiciously large vicinal coupling constant (10 Hz). Trisubstituted phenethylamines may only form vicinally-derived doublets in the aromatic region if the phenyl substituents are arranged such that the two aromatic protons are *alpha* to each other.

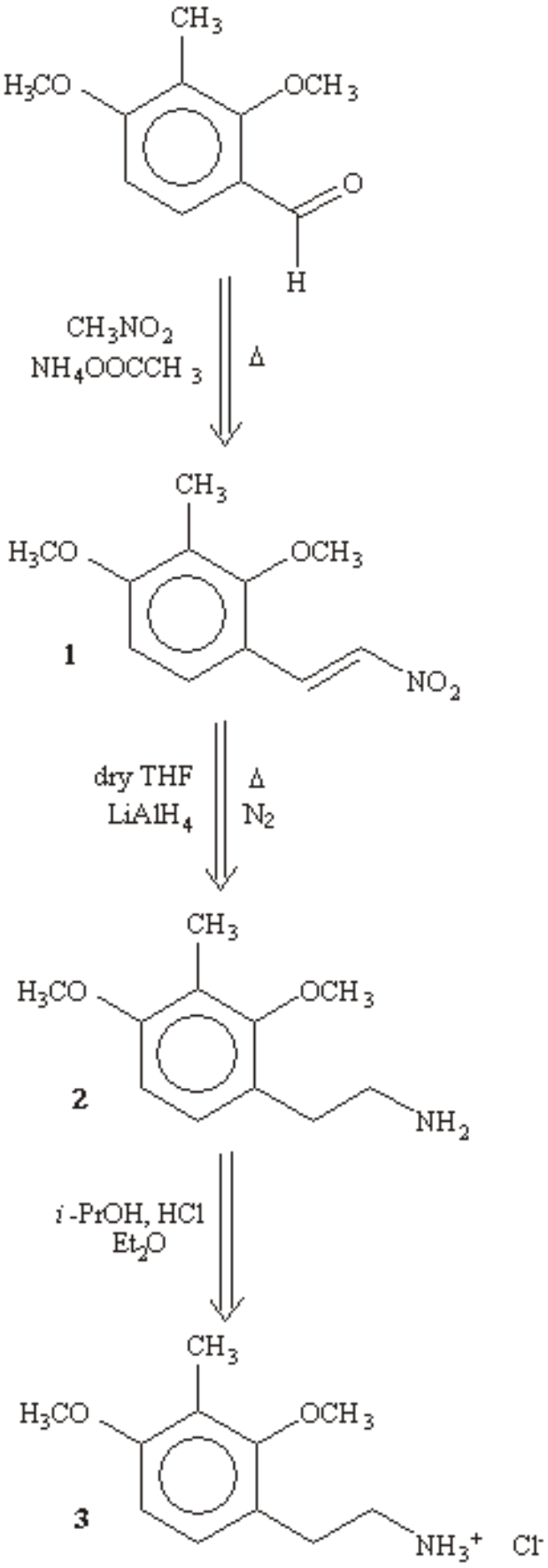
An example of an isomer of 2C-D having adjacent phenyl protons is 2,4-dimethoxy-3-methylphenethylamine HCl (**3**).[2] While NMR spectral differences between **3** and 2C-D can be predicted, it was preferable to demonstrate these differences from actual data.

The synthesis of 2,4-dimethoxy-3-methyl-β-nitrostyrene (**1**), 2,4-dimethoxy-3-methylphenethylamine (**2**), and **3** was originally reported by Merchant, *et al*.[2] and is provided herein along with new spectroscopic data (Scheme 1). In addition, the analytical results are compared to those of the recently received 2C-D exhibit.

Experimental

Reagents: All reagents and solvents were obtained from commercial sources and unless otherwise noted were used as received. Tetrahydrofuran was dried with Na/benzophenone and distilled under nitrogen prior to use.

Scheme 1.


CH3
H3CO
OCH3
O
H
CH3NO2
NH4OOCCH3
Δ
CH3
H3CO
OCH3
1
NO2
dry THF
LiAlH4
Δ
N2
CH3
H3CO
OCH3
2
NH2
i-PrOH, HCl
Et2O
CH3
H3CO
OCH3
3
NH3+
Cl-

Instrumentation: FTIR spectra were recorded on a Nexus 470 FTIR Spectrometer fitted (where noted) with a 3-bounce diamond ATR from SensIR Technologies. ^{1}H and $^{13}C\{^{1}H\}$ (proton-decoupled) NMR spectra were recorded at 24(±1) ^{O}C on a Varian Mercury 400 NMR Spectrometer. Chemical shifts (in ppm) are referenced to the residual solvent peak ($CHCl_3$, ^{1}H: δ 7.24 (singlet); (CHD_2OD, ^{1}H: 3.30 (quintet); $CDCl_3$, $^{13}C\{^{1}H\}$: 77.0 (triplet); CD_3OD, $^{13}C\{^{1}H\}$: δ 49.0 (septet) ppm). Mass spectral data were obtained from an Agilent 6890 Gas Chromatograph equipped with a ZB-1 column of 30 m x 0.25 mm with a film thickness of 0.25 μm, and equipped with an Agilent 5973N Mass Selective Detector in electron impact mode. The GC had an injector temperature of 250 ^{O}C, and was oven programmed with initial temperature of 100 ^{O}C increased at 35 ^{O}C per minute to 295 ^{O}C (held 6.43 min). The mass spectrum was scanned from *m/z* 34 to 500.

2,4-Dimethoxy-3-methyl-β-nitrostyrene (1-(2,4-dimethoxy-3-methylphenyl)-2-nitroethene) (1): To a nitromethane solution (30 mL) of anhydrous ammonium acetate (1.0 g, 13 mmol) was added 2,4-dimethoxy-3-methylbenzaldehyde (8.0 g, 44 mmol). The resulting mixture was stirred and heated for 20 minutes at light reflux. The solvent was then removed under reduced pressure (via rotary evaporator) while warming. The resulting orange solid was recrystallized from isopropanol, collected by vacuum filtration, and dried under vacuum (8.3 g, 85% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (d, J=13.7 Hz, 1H), 7.72 (d, J=13.7 Hz, 1H), 7.34 (d, J=8.8 Hz, 1H), 6.69 (d, J=8.6 Hz, 1H), 3.87 (s, 3H), 3.74 (s, 3H), 2.15 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 162.4, 159.8, 136.0, 135.5, 129.1, 121.0, 116.3, 106.8, 61.3, 55.9, 9.0 (11 signals expected and observed) ppm. FTIR (KBr, cm^{-1}): 1621 ($\nu_{C=C}$ str), 1597 ($\nu_{aromatic\ C=C}$ str), 1334 (ν_{NO2} sym str), 1109 (ν_{C-O-C} sym str). FTIR (ATR, cm^{-1}): 1622 ($\nu_{C=C}$ str), 1591 ($\nu_{aromatic\ C=C}$ str), 1336 (ν_{NO2} sym str), 1107 (ν_{C-O-C} sym str). GC/MS: Rel. Rt: 2.00 (relative to methamphetamine), *m/z* (assignment): 223 (M^{+}), 176 (base peak).

2,4-Dimethoxy-3-methylphenethylamine (2): To a 500 mL round bottom flask was added 2.1 g $LiAlH_4$ (56 mmol) and 70 mL dry THF. Under a nitrogen atmosphere was slowly added (via an addition funnel) 2.5 g **1** (11 mmol) dissolved in 60 mL dry THF. The resulting solution was heated at reflux with stirring under a nitrogen atmosphere for 7 hours. After cooling the reaction mixture to ambient temperature, an equal volume of water (130 mL) was added, with the initial addition being done drop wise to minimize the vigorous reaction. The reaction mixture was extracted with EtOAc (4 x 90 mL); each extract was dried with Na_2SO_4, filtered, and combined. Removal of the solvent under reduced pressure resulted in a pale yellow oil as the crude product. This oil was redissolved in 10 mL CH_2Cl_2 and extracted with several fractions (3 - 4 mL each) of aqueous HCl (pH 2-3) until the pH of the final aqueous fraction did not increase (the latter was discarded). The combined aqueous fractions were base extracted with 2 M NaOH and CH_2Cl_2. The organic layer was collected and removal of the solvent under reduced pressure yielded 1.3 g of a clear oil (58% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.95 (d, J=8.2 Hz, 2H), 6.57 (d, J=8.4 Hz, 2H), 3.77 (s, 3H), 3.68 (s, 3H), 2.89 (t, J=7.0 Hz, 2H), 2.69 (t, J=7.0 Hz, 2H), 2.13 (s, 3H), 1.8 (br-s, N-H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 157.5, 157.2, 127.2, 124.5, 119.6, 106.0, 60.6, 55.5, 43.1, 34.0, 9.1 (11 signals expected and observed) ppm. FTIR (neat/NaCl, cm^{-1}): 3366 (ν_{NH} str), 3296 (ν_{N-H} str), 1602 (ν_{N-H} bend), ~1590 (sh, $\nu_{aromatic\ C=C}$ str), 1268 (ν_{C-N} str), 1108 (ν_{C-O-C} sym str). FTIR (ATR, cm^{-1}): 3371 (ν_{N-H} str), 3289 (ν_{N-H} str), 1601 (ν_{N-H} bend), ~1590 (sh, $\nu_{aromatic\ C=C}$ str), 1266 (ν_{C-N} str), 1103 (ν_{C-O-C} sym str). GC/MS: Rel. Rt: 1.57 (relative to methamphetamine), *m/z* (assignment): 195 (M^{+}), 166 (base peak).

2,4-Dimethoxy-3-methylphenethylamine HCl (3). To a test tube of 0.34 g **2** (1.8 mmol) dissolved in ~6 mL isopropanol was added 5-6 drops of concentrated HCl and mixed well. Crystallization was induced by addition of 0.5 mL Et_2O and cooling to ~2 ^{O}C for 2 hours. The resulting mixture was decanted, and the resulting crystalline solid was rinsed with diethyl ether and dried under vacuum, yielding 0.25 g of a white crystalline solid (63% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32 (br-s, N-H, 3H), 7.00 (d, 8.4 J=8.4 Hz, 1H), 6.57 (d, J=8.2 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.22 (br-m, 2H), 3.01 (t, J=7.1 Hz, 2H), 2.11 (s, 3H); ^{1}H NMR (CD_3OD, 400 MHz): δ 7.05 (d, J=8.4 Hz, 1H), 6.71 (d, J=8.4 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.11 (t, J=7.6 Hz, 2H), 2.91 (t, J=7.6 Hz, 2H), 2.13 (s, 3H); $^{13}C\{^{1}H\}$ NMR (CD_3OD, 100.6 MHz): δ 159.7, 158.8, 128.9, 122.6, 120.9, 107.6, 61.3, 56.1, 41.6, 29.4, 9.4 (11 signals expected and observed) ppm. FTIR (KBr, not assigned). FTIR (ATR, not assigned).

Results and Discussion

Synthesis of **1** involved a condensation/dehydration of the precursor 2,4-dimethoxy-3-methylbenzaldehyde with nitromethane in the presence of ammonium acetate (Scheme 1). Recrystallization from isopropanol provided yellow crystals of **1** in good yield. The mass spectrum of **1** (Figure 1) is consistent with its structure.

The ^{1}H NMR spectrum of **1** (Figure 2) is consistent with formation of the expected, more stable *trans* isomer as evidenced by downfield chemical shifts and relatively large vicinal coupling constants compared to those typically found in the *cis* counterparts. The coupling constants for the alkene protons are slightly depressed with respect to comparable *trans* compounds due to the added electron-withdrawing effect of the nitro group.

The IR (Figures 3 and 4) spectral assignments also support the *trans* isomer of **1** based upon the work of By *et al*.[3] (wherein related β-methyl-β-nitrostyrenes were compared and characterized by IR/Raman spectroscopy). Notably, the lower frequency for the ethylenic C=C stretching mode of **1**, compared to the β-methyl-β-nitrostyrenes, can be accounted for by increased conjugation with the aromatic ring in the absence of the sterically hindering β-methyl group, allowing for a more planar conformation. On the other hand, the higher frequency observed for the symmetric NO_2 stretching band of **1** can be explained by the absence of the electron donating β-methyl group.

The free base form of **2** was obtained from reduction of **1** with $LiAlH_4$ in dry THF under an inert atmosphere (Scheme 1). The crude oily product obtained after work up of the reaction mixture was shown to contain minor amounts of impurities. Surmising that the desired product might have differing pKa value(s) from those of the impurities, **2** was successfully isolated by acid extraction with careful control of pH, followed by basic extraction. The MS, FTIR, ^{1}H NMR spectra (Figures 5, 6, and 7, respectively) were consistent with the formation of **2**.

Conversion of **2** to its hydrochloride salt was done from an isopropanolic solution mixed with a small amount of concentrated hydrochloric acid and diethyl ether, yielding a white, crystalline solid (Scheme 1) of **3**. The IR spectra of **3** (Figures 8 and 9) are complicated by the broad and numerous bands displayed, particularly in the region between 3500 - 2000 cm^{-1}, as is expected for hydrated primary amine salts.[4]

The ^{1}H NMR spectrum (Figure 10) exhibits a broad peak for the protonated amine at 8.32 ppm. Despite extensive drying of the crystalline material under vacuum, a water peak is still observed at ~1.7 ppm, likely due to the inclusion of a hydrogen bonded water molecule in the crystalline lattice of **3**, suggesting the formation of a hydrate complex upon crystallization. Addition of 1 - 2 drops CD_3OD to a $CDCl_3$ solution of **3** results in a shift of the H_2O peak downfield ~1.5 ppm as CD_3OH is formed. In CD_3OD, the ^{1}H NMR spectrum (Figure 11) of **3** lacks peaks for the exchangeable amino and water protons. Due to a reduced solubility relative to **2** in chloroform solution, the ^{13}C NMR spectrum of **3** was obtained in deuterated methanol.

Not surprisingly, the FTIR and mass spectra of **3** and 2C-D are fairly similar. However, differences in the substitution patterns on the phenyl ring make these compounds readily distinguishable by ^{1}H NMR, as displayed in the spectrum (Figure 12) of the 2C-D exhibit received into this lab. The most distinguishing features are the two singlets of the phenyl protons in the spectrum of 2C-D, at 6.69 and 6.66 ppm, whereas **3** displays two doublets at 7.00 and 6.57 ppm, respectively.

It should be noted that closely related analogues such as 2,3,4-trimethoxyphenethylamine (also known as "isomescaline") and 2,4-dimethoxy-3-thiomethylphenethylamine (also known as "TIM") have been reported to be "non-active" (that is, having no noticeable pharmacological effects on the user.[1]) The isostructural nature of **3** with these pharmacologically inactive compounds suggests that it is likewise inactive. However, because other dimethoxy/methyl-substituted phenethyamine isomers of **3** (e.g., 2C-D and DESOXY) are psychoactive, the situation is unclear. Regardless, these and other possible isomers can be readily distinguishable by NMR.

Acknowledgments

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References

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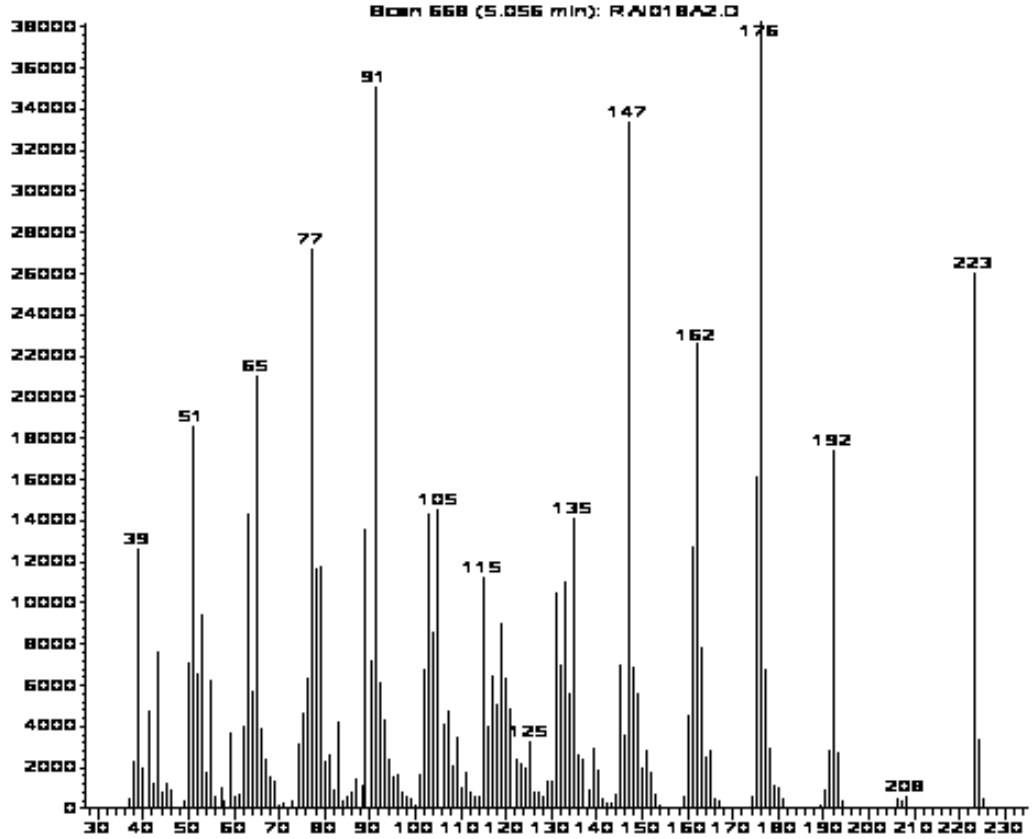

Figure 1. Mass Spectrum of **1**.

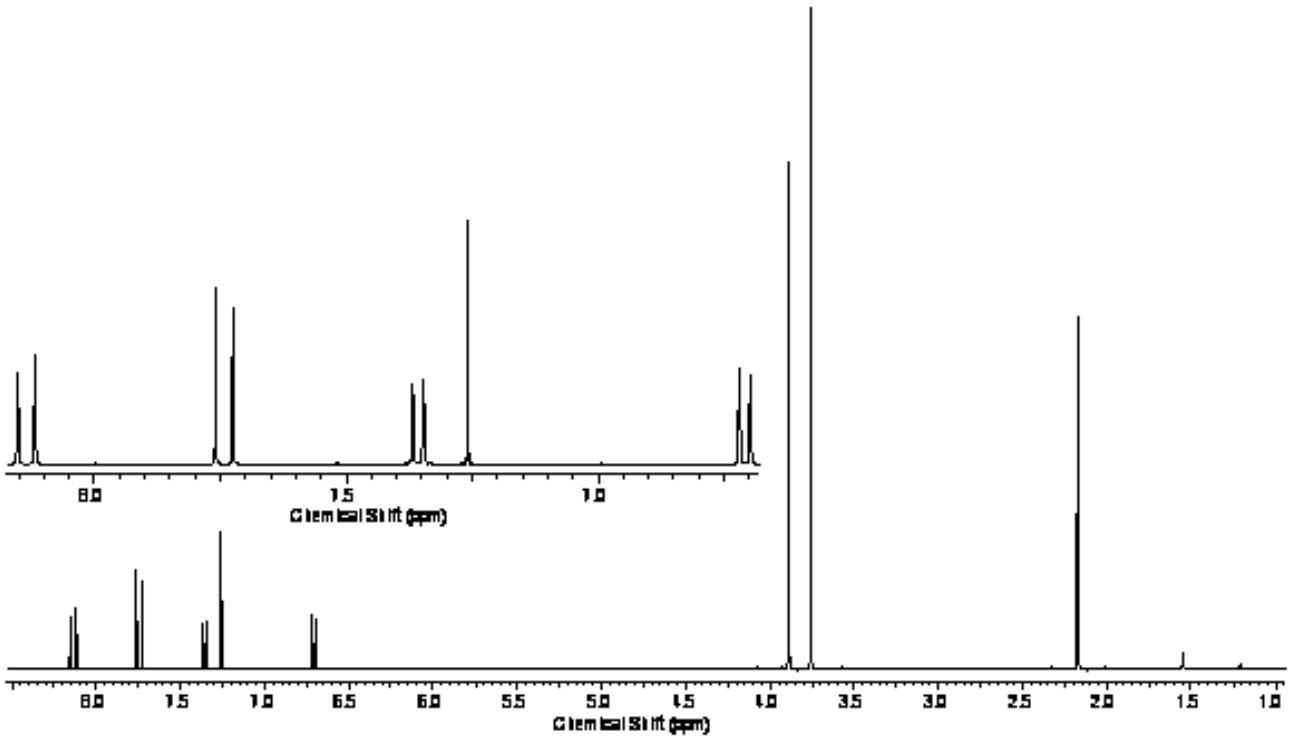

Figure 2. ^{1}H NMR Spectrum of **1** in $CDCl_3$.

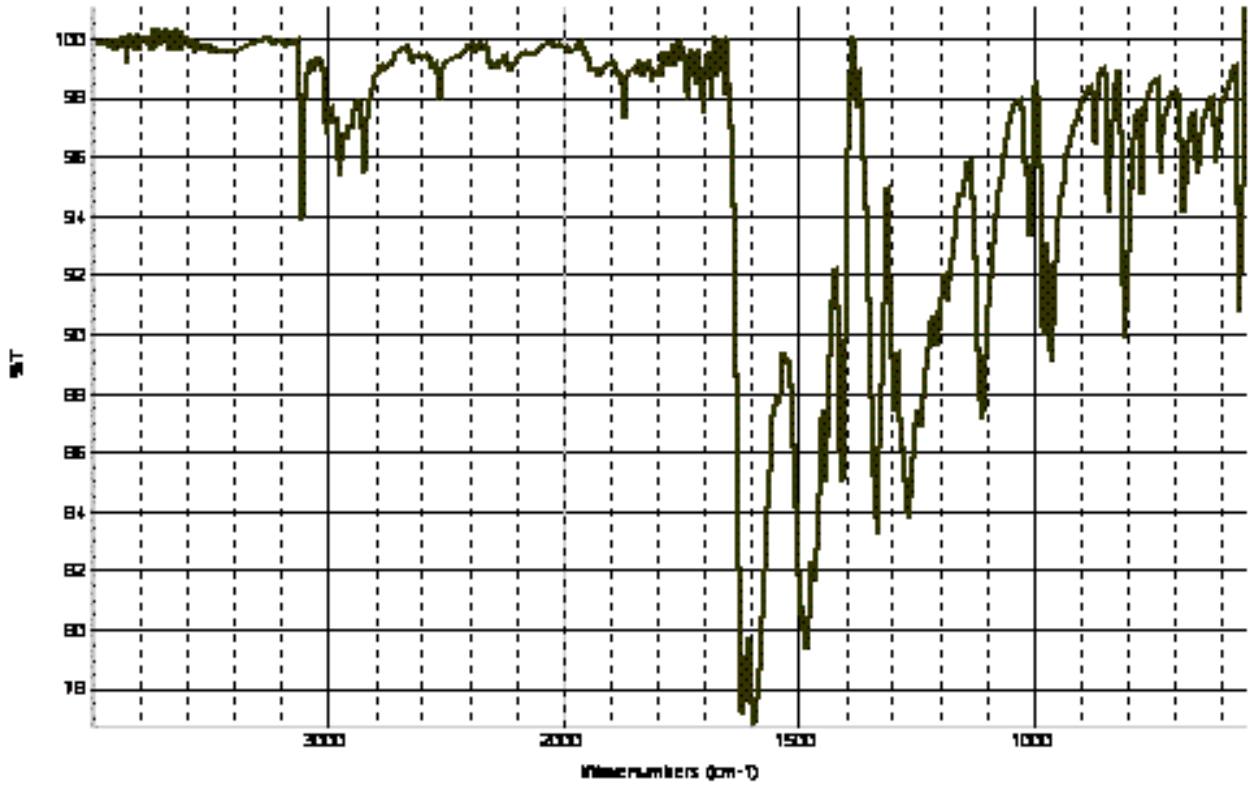

Figure 3. FTIR (KBr) Spectrum of **1**.

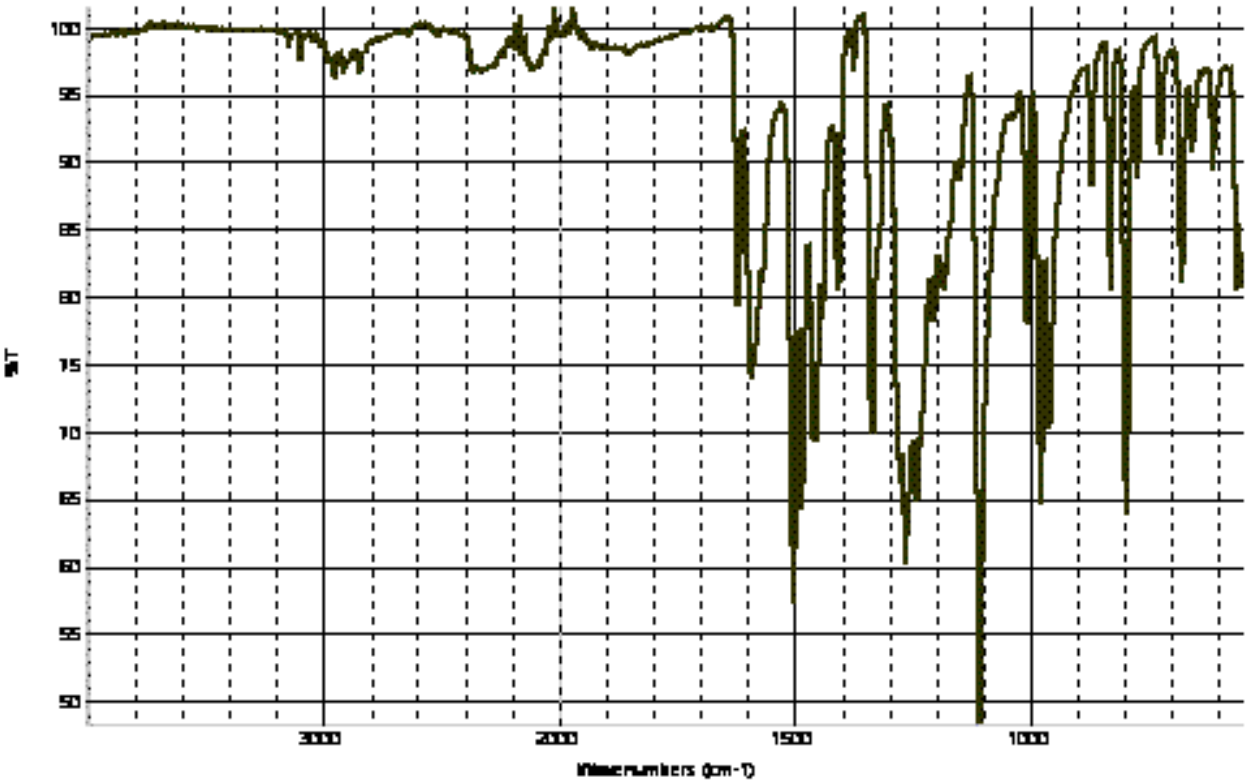

Figure 4. FTIR (ATR) Spectrum of **1**.

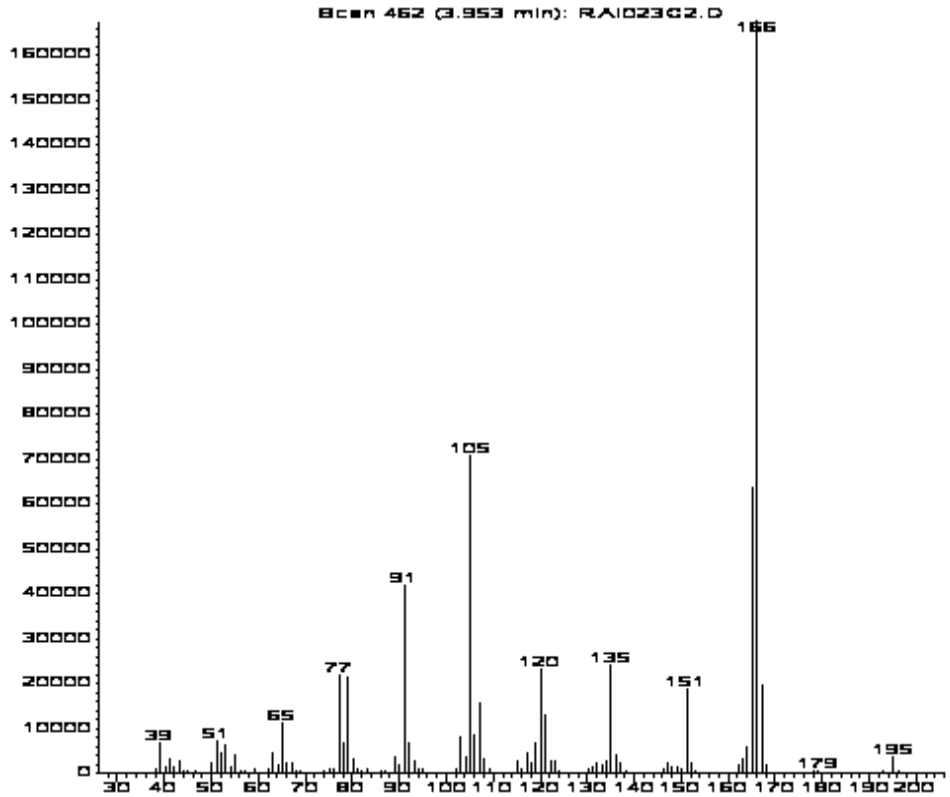

Figure 5. Mass Spectrum of **2**.

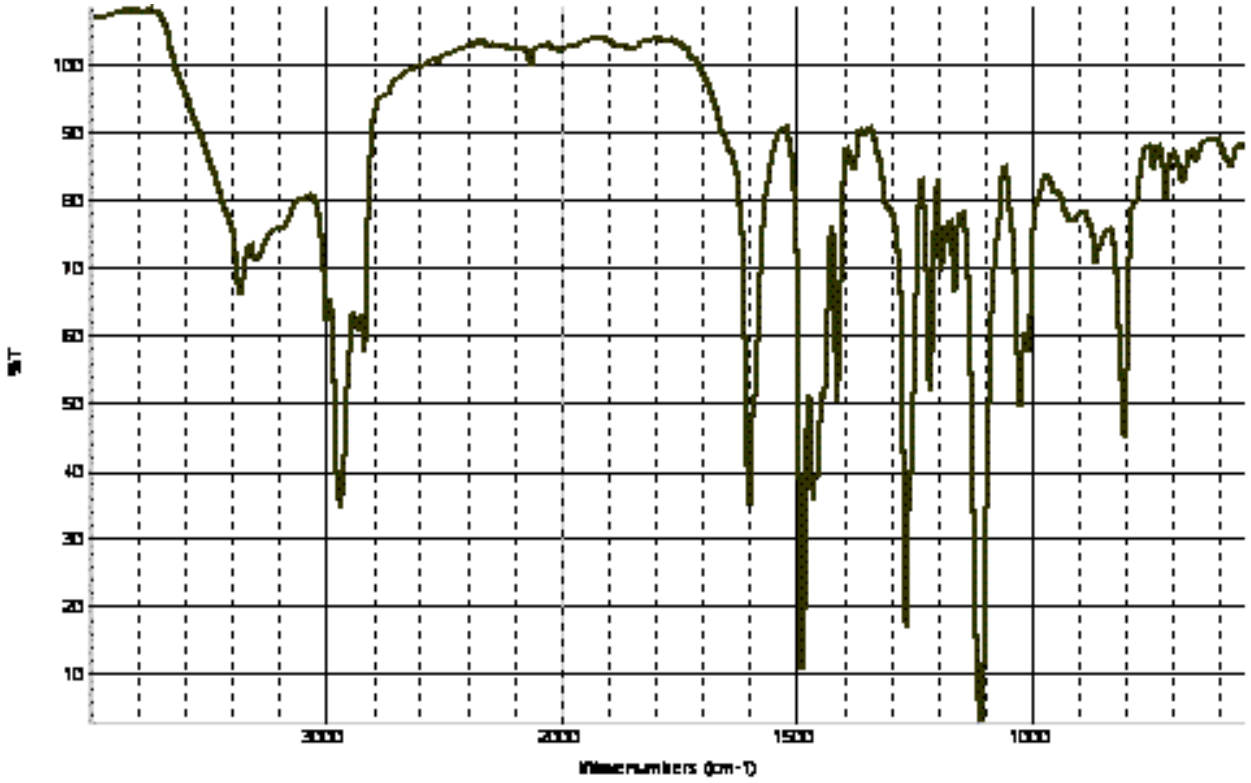

Figure 6. FTIR (Neat, NaCl) Spectrum of **2**.

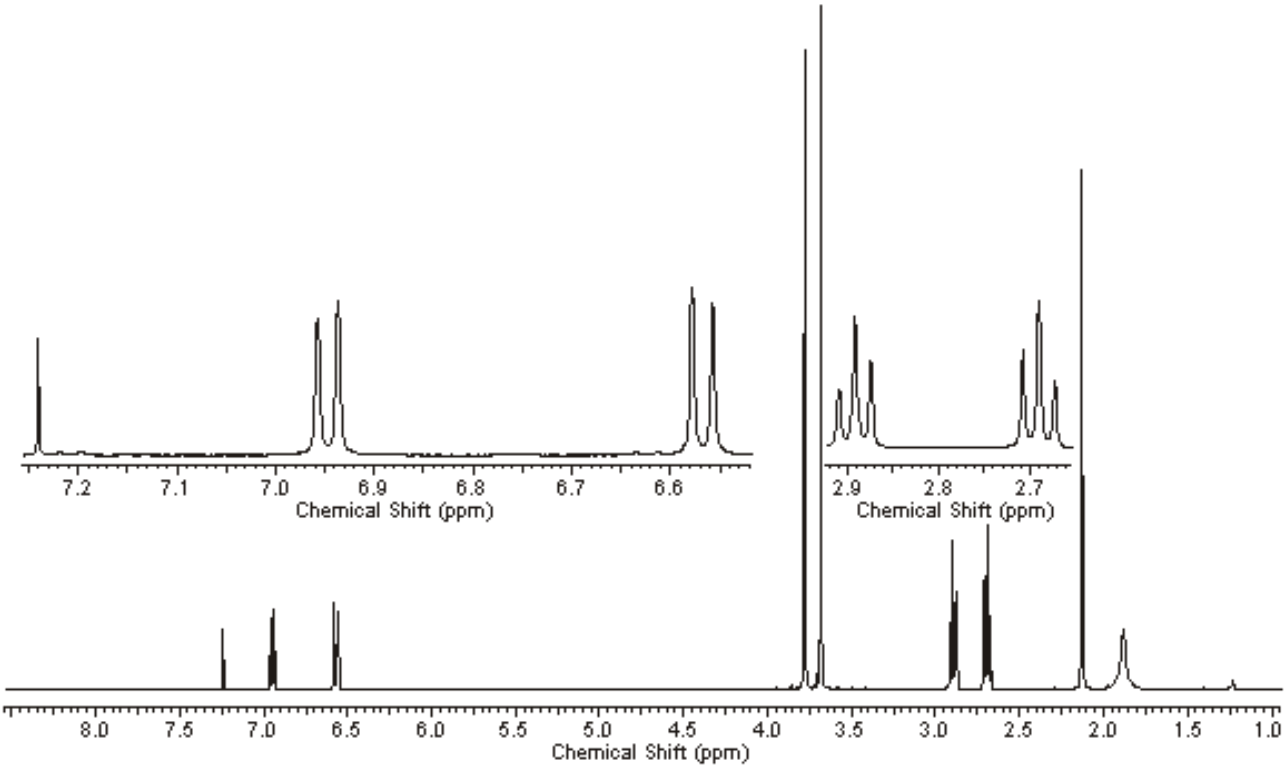

Figure 7. ^{1}H NMR Spectrum of **2** in $CDCl_3$.

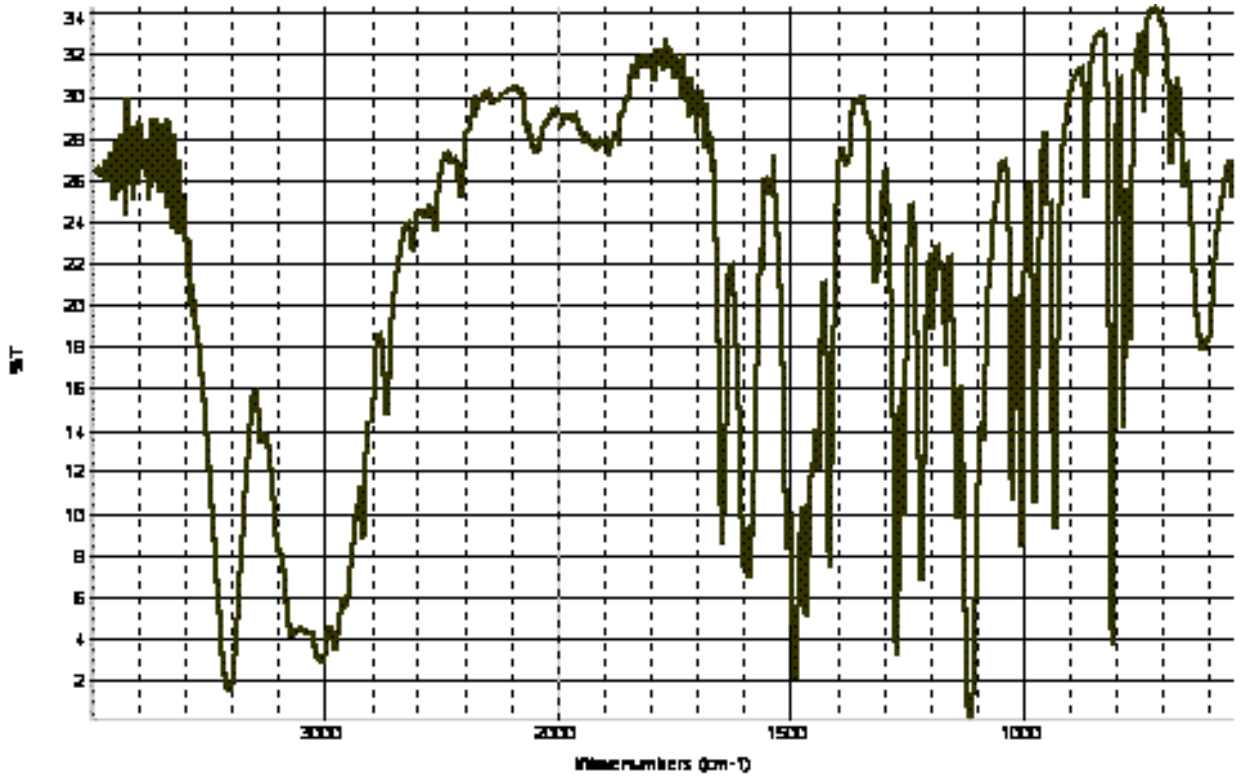

Figure 8. FTIR (KBr) Spectrum of **3**.

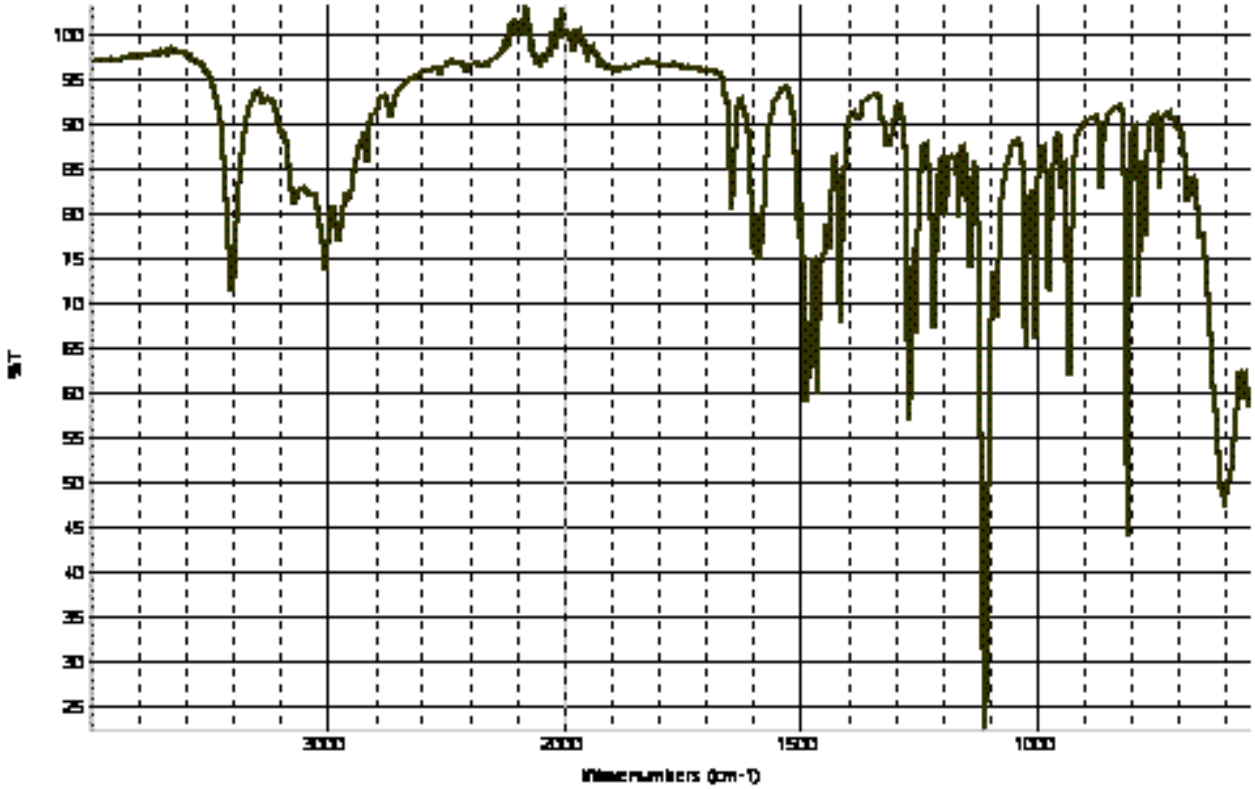

Figure 9. FTIR (ATR) Spectrum of **3**.

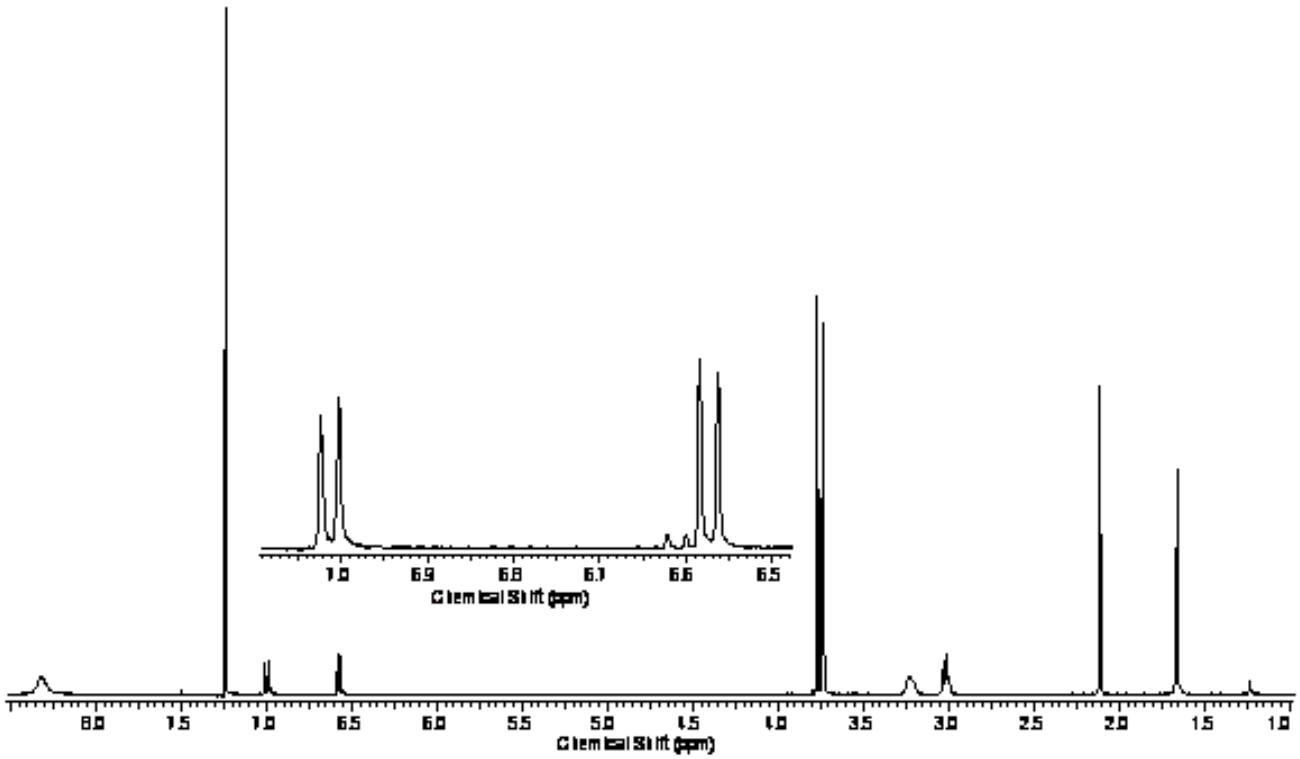

Figure 10. ^{1}H NMR Spectrum of **3** in $CDCl_3$.

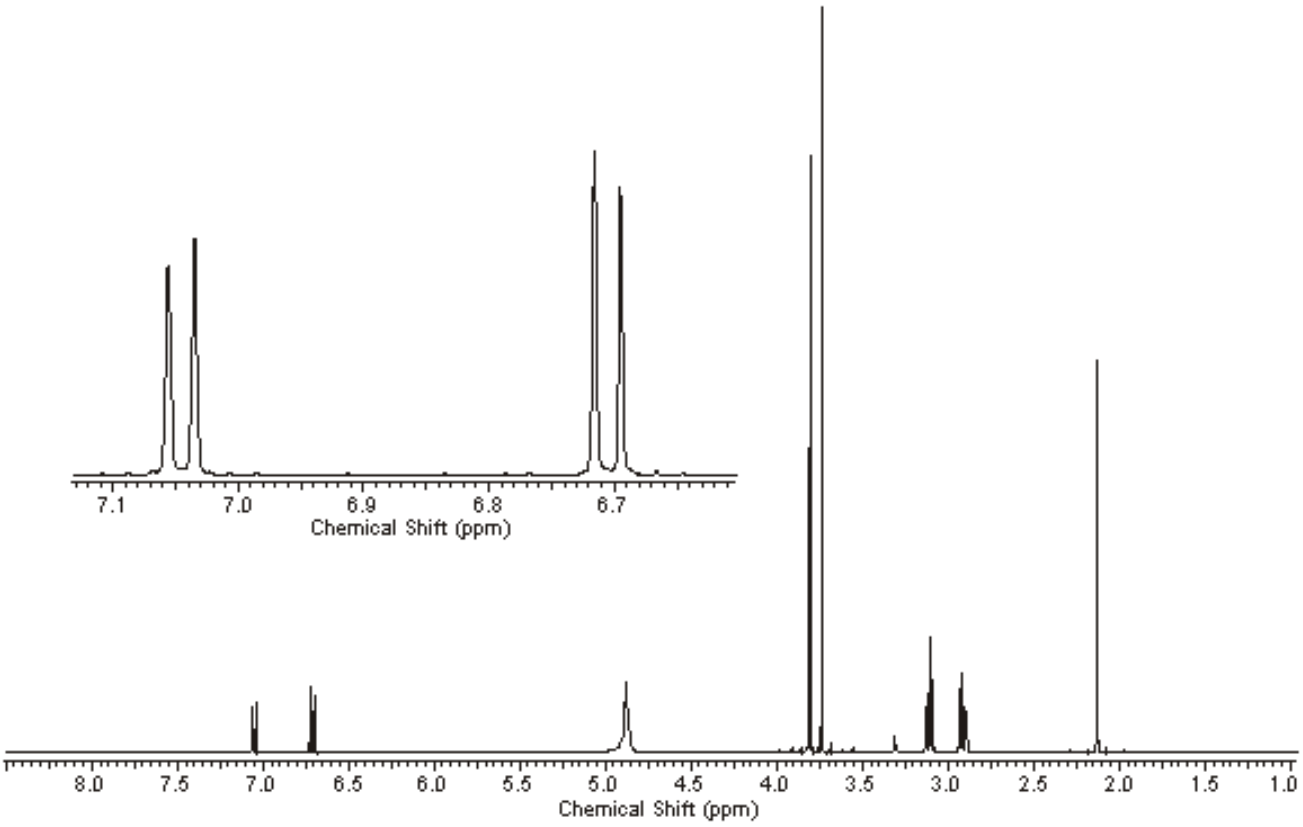

Figure 11. ^{1}H NMR Spectrum of **3** in CD_3OD.

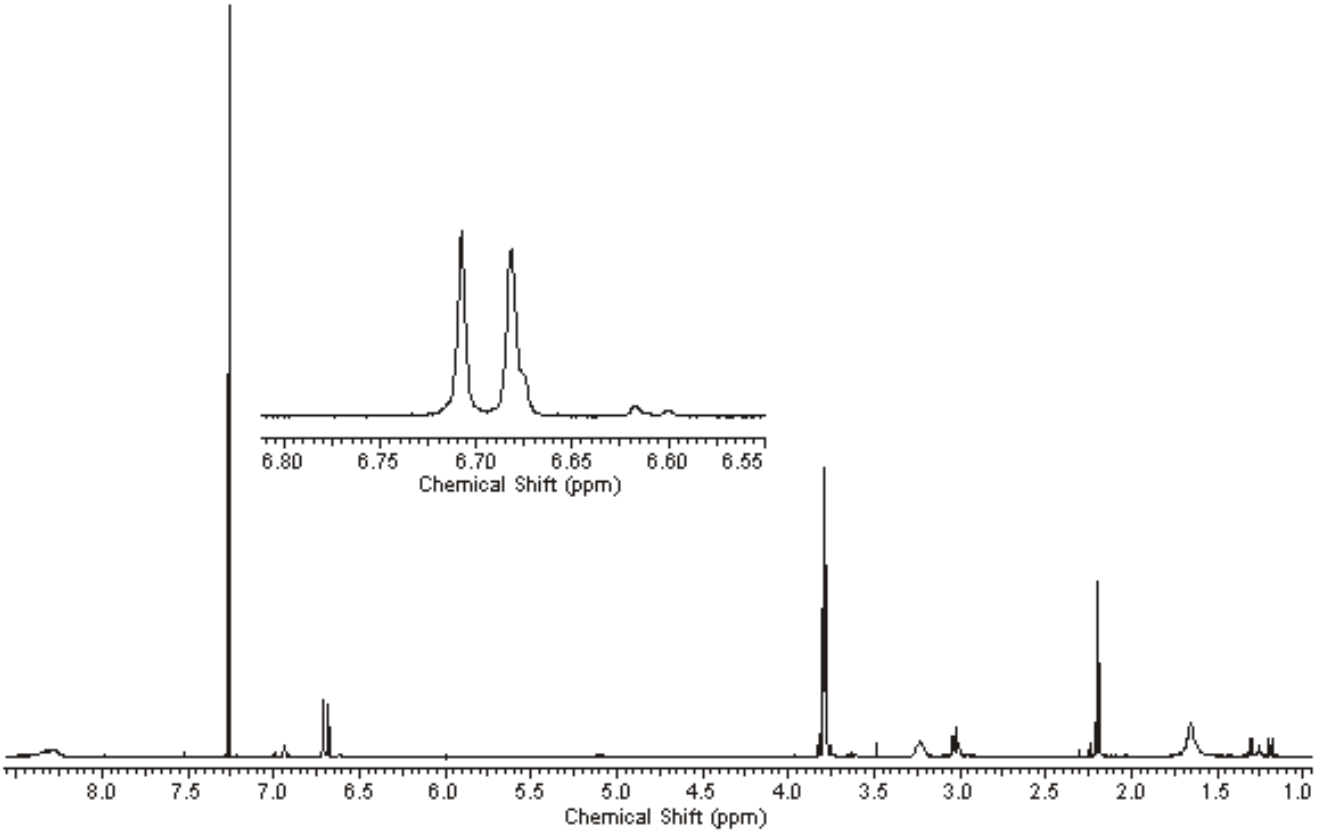

Figure 12. ^{1}H NMR Spectrum of a 2C-D Exhibit in $CDCl_3$.

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