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CHEM 4420

Synthesis of N,N-diethyl-2-[(trimethylsilyl)methyl] benzamide by a Directed Lateral Lithiation Reaction

Submitted March 13th, 2022

ABSTRACT:

The synthesis of N,N-diethyl-2-methylbenzamide, 91.0 % yield, and N,N-diethyl-2-[(trimethylsilyl)methyl] benzamide, 75.8 % yield, through a nucleophilic acyl substitution reaction and directed lateral lithiation reaction is presented. A fundamental structure type, found within both synthesized compounds, has been previously reported to present strong antifungal properties. This specific molecular geometry consists of steric hindrance which inhibits free bond rotations within the compound. ^{1}H and ^{13}C NMR spectroscopy was implemented and used as a tool to observe the steric hindrance present within the compounds, successfully determining the drug activity of the compounds synthesized. FT-IR spectroscopy was utilized to further elucidate the structure of starting material (**5a**) and the purity of crude product (**7a**) was assessed by TLC. This study demonstrates a directed lateral lithiation reaction in the synthesis of N,N-diethyl-2-[(trimethylsilyl)methyl] benzamide and reports the efficacy of synthesized compounds N,N-diethyl-2-methylbenzamide and 2-methyl-N-butyl-N-ethylbenzamide as antifungal drugs.

INTRODUCTION:

The metalation of organic compounds has seen widespread use in synthetic laboratories due to its significant contributions in research and industrial chemical reactions. The process, first completed in 1757 by French chemist Louis Claude de Gassicourt, involves bonding a metal to an organic compound, synthesizing an organometallic complex.[1] The directed *ortho*-Metalation, DoM, strategy, first reported in 1940 by both Gilman and Wittig, is known as an adaptation of the electrophilic aromatic substitution reaction.[2] This reaction, shown in Scheme. 1, involves a strong base which deprotonates the site *ortho* to a directing metalation group, DMG, allowing an electrophile to bond exclusively to the *ortho* position. In 1990, Victor Snieckus established a hierarchy of DMG's according to their directing abilities and his review is considered a valuable resource for synthesis preparation of substituted aromatics.[3] The DoM approach provides an efficient and regioselective method to synthesize highly substituted aromatic compounds.

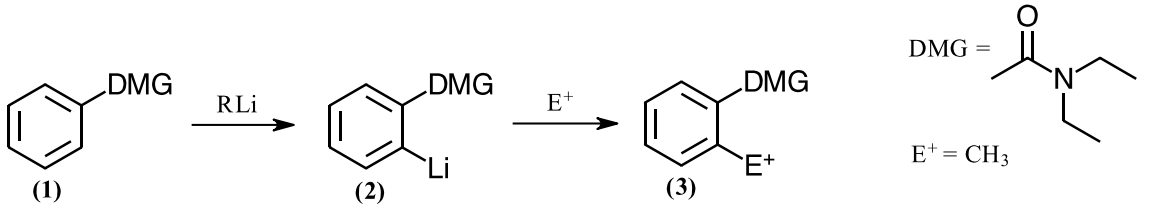
For further functionalization of inactivated aromatic *ortho* alkyl groups, directed *ortho*- or lateral lithiation reactions can be carried out, as shown in Scheme. 2. These reactions involve the lithiation of *ortho* alkyl groups, synthesizing organolithium complexes, which can serve as a nucleophile for further reactions. The reaction completed in this analysis demonstrated a lateral lithiation, rather than an *ortho* lithiation, which is shown to have a greater thermodynamic stability.[4] The difference between the methods rests on the effect the acidifying group will operate on, being either the inductive effect or conjugation for *ortho* - and lateral lithiation respectively.[4]

Previous studies found Silthiofam and compound (**7**), who share structural properties, present significant antifungal properties due to the steric crowding between the trimethylsilyl (TMS) group and the tertiary amide.[5] This existing steric hindrance can slow down the free bond rotation within the bond between the aromatic carbon and the carbonyl carbon, as well as the carbon-nitrogen bond. However, unlike Silthiofam, the presence of a benzylic carbon separating the TMS complex, and the aromatic ring has the potential to affect the amount of rotational

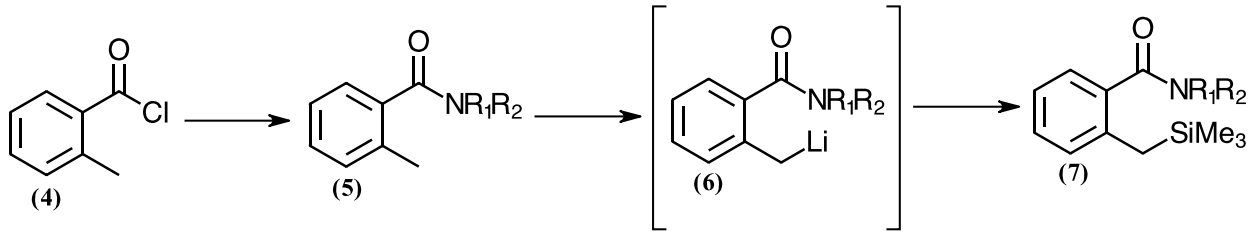
hindrance and therefor produce major differences in the activity of a drug. This difference in bond rotation can be observed in NMR spectra through couplings attached to the amide nitrogen.

This report aims to provide an extensive methodological investigation of a directed lateral lithiation reaction as well as determine compounds (**5a**) and (**5b**)'s biological activity as a fungicide. The synthesis of starting material, N,N-diethyl-2-methylbenzamide (**5a**), and crude product, N,N-diethyl-2-[(trimethylsilyl)methyl] benzamide (**7a**) was carried out firstly by a nucleophilic acyl substitution reaction and secondly by a directed lateral lithiation reaction, as detailed in Scheme. 2. The thin layer chromatography, TLC, technique was also employed to determine the purity of the crude product (**7a**). Further, the characterization of compounds (**5a**) and (**5b**) through IR spectroscopy as well as ^{1}H and ^{13}C NMR spectroscopy was utilized to determine drug activity and is described below.

Scheme. 1 The directed *ortho*-metalation reaction.



Scheme. 2 Directed lateral lithiation reaction.



(**5a**), (**7a**) R_1= R_2= Ethyl

(**5b**), (**7b**) R_1= 1-Butyl, R_2= Ethyl

RESULTS AND DISCUSSION:

Synthesis of 5a. N,N-diethyl-2-methylbenzamide was obtained by a nucleophilic acyl substitution reaction of o-toluoyl chloride. The strong base, triethylamine was added in 1.05 equiv. to neutralize the by-product hydrogen chloride producing a stable salt. The addition of 1.05 equiv. of diethylamine then caused the addition/elimination process, with the electrons of the nitrogen attacking the electrophilic carbonyl carbon of the o-toluoyl chloride, resulting in the removal of the chlorine atom and a newly formed carbon-nitrogen bond. This reaction had an overall yield of 91.0 %.

Compound (**5a**) was first characterized by FTIR, as shown in Figure. 1. The resulting spectrum revealed a peak stretch at 1627.74 cm^{-1} which can be assigned as a carbonyl stretch.

The spectral data from the ^{1}H NMR, shown in Figure. 3, indicated two triplets were the furthest upfield peaks, located at 1.0254 ppm and 1.2589 ppm. These peaks represent the two CH_3 groups on the diethylamine coupling to the adjacent CH_2 groups due to their integrations of 3 as well as their up-field portrayal, a result of their distance from the nitrogen. As well, due to the rotation of the bond between the carbonyl carbon and the nitrogen, these CH_3 groups are in non-equivalent environments, producing two triplets instead of a single triplet. The singlet evident at 2.2856 ppm can be assigned to the *ortho* substituted methyl group due to its integration of 3, as well as its inability to couple to any other protons which produces a singlet. The quartet at 3.1192 ppm as well as the two undistinguishable bumps at 3.4121 and 3.7565 ppm, shown in Figure. 4, can be attributed to the methylenes on the diethylamine due to their individual integrations of 2. These peaks are shown so far upfield due to its proximity to the electronegative nitrogen, which is deshielding the protons. Further analysis can be conducted to determine the exact assignment of each signal. The two lumps present at 3.4121 and 3.7656 ppm can be assigned to the two protons of one of the CH_2 groups. Its indistinguishability is due to the restricted rotation of the molecule placing a CH_2 in proximity of the large *ortho* substituted methyl group. This methyl group therefore sterically hinders the CH_2 and conceals the predicted splitting pattern, a quartet. The quartet present at 3.1192 ppm can therefore by assigned to the methylene on the diethylamine that is the furthest away from the sterically hindering *ortho* -substituted methyl group. Finally, also shown in Figure. 4, the most up-field resonances are at 7.1990 ppm and can be assigned to the four protons attached to the benzene due to its integration value of four as well as the resonance being in the aromatic range of the ^{1}H NMR spectra.

Compound (**5a**) was further characterized by ^{13}C $\{^{1}H\}$ NMR spectroscopy as shown in Figure. 5. Beginning at the most upfield peaks, the two peaks shown at 15 ppm can be assigned to the two non-equivalent CH_3 groups on the diethylamine. The *ortho* substituted methyl group represents the next peak at 18 ppm. Due to the de-shielding effect of the nitrogen, the two CH_2 groups, also non-equivalent, can be assigned to the two peaks at 40 ppm. The two CH_2 groups are in non-equivalent environments due to the restricted rotation of the bond between the carbonyl carbon and the nitrogen. Further, the peak shown at 77 ppm can be assigned to the solvent, being $CDCl_3$. As deuterium has a spin multiplicity of 1, this peak is split into a triplet. The aromatic region of the spectra illustrates 6 singlets between 120 and 140 ppm, demonstrating the resonances of the six unique aromatic carbons. Of the six illustrated peaks, the two most downfield peaks are shown significantly smaller than the other four. These peaks represent the carbons with no hydrogens attached as due to relaxation effects, the carbons with hydrogens attached are known to have stronger signals. Further, characterization of the two weak signals can be done since the furthest downfield peak, at 137 ppm, can be assigned to the aromatic carbon bonded to the carbonyl

carbon. The carbonyl oxygen de-shields this carbon more so than the methyl group attached to the aromatic carbon shown at 133 ppm. Due to this extreme de-shielding effect, the carbonyl carbon is portrayed as the furthest downfield singlet, at 170 ppm.

Synthesis of 5b. 2-methyl-N-butyl-N-ethylbenzamide was also synthesized by a nucleophilic acyl substitution reaction of o-toluoyl chloride with 1.05 equiv. of a strong base, triethylamine, and 1.05 equiv. of N-ethyl-N-butylamine.

This compound was characterized initially by a ^{1}H NMR spectrometer. Due to the restricted rotation within the molecule, each CH_2 and CH_3 compound is placed in non-equivalent environments which results in two different resonances for each proton signal, as shown in Figure. 7. Beginning in the up-field region of the spectra, the two triplets presented at 0.7457 ppm and 0.9783 ppm can be assigned to the CH_3 of the butyl ligand. The proton signal for the CH_3 of the ethyl ligand is also shown as two triplets at 1.0014 and 1.2497 ppm, further downfield compared to the butyl CH_3 because of its nearness to the nitrogen. Due to the proximity of the triplets at 0.9783 and 1.0014 ppm, the integrations were combined resulting in a total of 3. By dividing 3 in half, 1.5 for each triplet, and adding to the 1.5 from the triplets at 0.7457 and 1.2497 ppm, results in an integration of 3 for each of these CH_3 groups.

Further, the resonance signal from the CH_2 directly adjacent to the CH_3 of the butyl group can be seen slightly further up-field, shown as a sextet at 1.0987, which is due to overlapping subpeaks of a triplet of quartets. The integration value calibrated for this resonance is 1. The second signal for this methylene is shown as overlapping one of the proton signals from the middle CH_2 of the butyl group, observed as a multiplet at 1.4163 ppm. Therefore, half of the integration value, being 2, can be attributed to the CH_2 adjacent to the CH_3 of the butyl group, whereas the other half can be assigned to the middle CH_2 of the butyl group. The other resonance associated with the middle CH_2 of the butyl chain is a signal produced at 1.6588 ppm with an integration of 1. Although this CH_2 should demonstrate a triplet of triplets, the spectra illustrates a splitting pattern of a quintet, which can be attributed to overlapping subpeaks within the signal. Adding the integration values from either the triplet of triplets, shown as a quintet, or sextet to half the integration of the multiplet successfully indicates 2 hydrogens are correlated with each CH_2 resonance.

Progressing downfield of the ^{1}H NMR spectra, the two doublets appearing at 2.2857 and 2.2742 ppm in Figure. 8 can be assigned to the proton resonances of the *ortho* positioned methyl on the aromatic ring. As well, the two quartets demonstrated at 3.1115 and 3.0404 ppm in Figure. 8 can be assigned to the single CH_2 of the ethyl chain. This groups proximity to the nitrogen shifted this resonance down field. When comparing the definition between the two signals, the signal demonstrated at 3.0404 is much less defined than the signal at 3.1115. This could be caused by the restricted rotation present within the molecule placing the less distinguishable quartet at 3.0404 in a more sterically hindered environment, effectively masking its associated coupling. Further, the CH_2 closest to the nitrogen of the buytl ligand demonstrates two undefined lumps at 3.7037 and

3.3763 ppm, also shown in Figure. 8. Similar to compound (**5a**), the indistinguishability of these resonances can be due to the restricted rotation placing the methylene in proximity of the *ortho* methyl group which obscures the proton splitting. The final peaks shown on the proton NMR, Figure. 6, is the multiplet at 7.1706, the most downfield resonance. Due to these peaks presenting in the aromatic region, it can be inferred these are the hydrogens on the aromatic ring, however, each hydrogen resonance cannot be distinguished from these spectral lines.

The ^{13}C {^{1}H} NMR spectroscopy of compound (**5b**) further allowed structural elucidation. Akin to the ^{1}H NMR of (**5b**), the hindered rotation present within the structure of this compound creates different environments and therefore two identical resonances for each carbon presented on the spectra. Shown as the most up-field resonances (Figure. 10) the peaks at 12.4061 13.2428 ppm can be assigned to the CH_3 of the butyl ligand. Next, the peaks demonstrated slightly more up-field, being 13.5024 and 13.6178 ppm, can be attributed to the CH_3 of the ethyl chain. The CH_3 of the ethyl chain is shown more up-field in comparison to the CH_3 of the butyl group due to its proximity to the nitrogen. Further, the methyl on the *ortho* position of the aromatic ring is shown at 18.4071 and 18.5514 ppm. The *ortho* CH_3 is further up-field than either the ethyl or methyl due to its proximity to the very electron withdrawing ring. The CH_2 adjacent to the methyl of the butyl ligand is shown at 19.4169 and 20.0517 ppm, whereas the middle CH_2 of the butyl chain is shown at 29.3418 and 30.3804 ppm. Proceeding downfield are the resonances of the two CH_2's closest to the nitrogen of either butyl or ethyl ligand. These peaks are demonstrated at 38.7185 and 42.5845 ppm for the butyl chain and 43.2770 and 43.3450 ppm for the ethyl chain. Due to the solvent utilized, $CDCl_3$, a peak is shown at 77 ppm in Figure. 9 which can be assigned to the resonance given by the associated carbon.

Akin to compound (**5a**), the six singlets shown between the ranges 120 and 140 ppm (Figure. 11) represent the aromatic carbons. Each signal is shown as a multiplet, indicating they are all in slightly different environments. The most upfield signals of the aromatic carbons, 125.1014 and 125.3033 ppm, can be assigned to the *para* carbon of the aromatic ring, due to its distance from any electron withdrawing groups. The *meta* carbon furthest from the methyl substituted *ortho* group, shown as the signals at 125.3437 and 125.3841 ppm is slightly more downfield than the *para*-carbon since it is closer to the carbonyl carbon. Further, the resonances at 128.1603 and 128.0895 ppm can be attributed to the methyl carbon closest to the *ortho* substituted methyl group. The most downfield unsubstituted aromatic carbon signals are shown at 129.8664 and 129.9371 ppm and can be assigned to the *ortho* unsubstituted carbon. The proximity of this carbon to the carbonyl carbon shifts the resonance downfield more so than the other unsubstituted carbons. The most downfield of the aromatic carbons is shown as weaker resonances at 133.3998, 133.4905, 136.7715 and 136.9836 ppm. As explained above, these signals are significantly weaker due to the absence of bonded hydrogens, which are known to strengthen the signal. Also, it was previously determined that due to the electron withdrawing effect from the carbonyl carbon, the most downfield signals of the aromatic carbons, 136.9836 and 136.7715 ppm, can be attributed to the carbonyl substituted by the carbonyl. This leaves the resonances at

133.3998 and 133.4905 to be attributed to the aromatic carbon bonded to the methyl group. Lastly, the two signals shown in Figure. 12 at 170 ppm can be assigned to the carbonyl carbon.

Synthesis of 7a. The synthesis of N,N-diethyl-2-[(trimethylsilyl)methyl] benzamide was completed through a benzylic lithiation and unimolecular substitution reaction of the starting material, compound (**5a**). Following the addition of the newly opened solvent, diethyl ether, 1.1 equiv. of TMEDA was added to coordinate with the lithium cation and prevent the formation of a clump of ionic salts. 1.1 equiv. of the organometallic compound sec-butylithium initiated the benzylic lithiation, attacking the acidic hydrogen on the ortho substituted methyl. The addition of the TMSCI, which acted as an electrophile to attack the lithiated arene, produced the by-product lithium chloride and the final product N,N-diethyl-2-[(trimethylsilyl)methyl] benzamide. The resulting yield of compound (**7a**) was 75.8 %. The TLC method was employed to determine the purity of the synthesized crude product compared to the starting material. As compound (**7a**) demonstrates a greater polarity, the retention factor was 0.52, observably larger than compound (**5a**)'s retention factor of 0.43.

CONCLUSION:

In summary, the synthesis of N,N-diethyl-2-methylbenzamide (**5a**), with a 91.0 % yield, and N,N-diethyl-2-[(trimethylsilyl)methyl] benzamide (**7a**), with a 75.8 % yield, was achieved by a nucleophilic acyl substitution reaction followed by a directed *ortho*-lithiation reaction. FT-IR spectrometry was utilized for initial structural characterization of starting material (**5a**). The characterizations by ^{1}H and ^{13}C NMR spectroscopy of starting materials (**5a**) and (**5b**) allowed for the determination of antifungal drug activity. Since unique environments were seen within both ^{1}H and ^{13}C NMR spectrums, in the form of multiple peaks for a specific signal, restricted rotation due to steric hindrance can be reported within these compounds. Therefore, it can be determined both compounds (**5a**) and (**5b)** present significant anti-fungal properties. Following characterization, TLC successfully demonstrated the purity of the final product (**7a**).

EXPERIMENTAL:

General Information. ^{1}H NMR (500 MHz) and ^{13}C $\{^{1}H\}$ NMR (500 MHz) spectra were obtained on a Bruker UltraShield 500 plus spectrometer in $CDCl_3$. The chemicals shifts are presented in **δ** (ppm) relative to tetramethylsilane, TMS. A Perkin Elmer FT-IR spectrometer was used to record infrared spectra.

Materials. All solvents and reagents utilized were purchased commercially and supplied by Thompson Rivers University.

Experimental Procedures. N,N-diethyl-2-methylbenzamide (**5a**). To a dry round bottom flask containing THF (250 mL), C_8H_7ClO was added (6.8 mL). The solution was cooled in an ice bath

and stirred. Through an attached pressure equalizing dropping funnel, Et_3N (7.6 mL) was added dropwise addition. Minimal amount of THF was used to rinse dropping funnel, followed by 5.6 mL $C_4H_{11}N$ via dropwise addition. Solution was removed from ice bath and stirred, or if needed agitated, for forty minutes. Mixture was rotary evaporated to near dryness, removing the THF. The solution was then re-dissolved in $C_4H_8O_2$ (200 mL) and H_2O (200 mL) and transferred to separatory funnel. The organic layer was washed with water (2 x 200 mL) followed by a wash of sodium chloride solution (2 x 50 mL). The organic layer was dried (Na_2SO_4) gravity filtered and placed on rotary evaporator. Minimal amount of $C_4H_8O_2$ was utilized to transfer solution to dried flask and placed on rotary evaporator, followed by the vacuum pump. The Kugelrohr distillation technique was performed on the crude product a week later, with a vacuum reading 0.0136 and temperature 95-96 ℃. Starting material (**5a**) produced a yellow viscous oil and provided a yield of 91.0 %. As compound (**5a**) has been reported in literature previously, most recently in 2021, it holds a CA name and number of N,N-Diethyl-2-methylbenzamide and 2728-04-3 respectively.[6] ^{1}H NMR (500 MHz, $CDCl_3$) **δ** (ppm) 1.03 (t, J = 15 Hz, 3H), 0.26 (t, J = 14.3 Hz, 3H), 2.29 (s, 3H), 3.14 (q, J = 8.0 Hz, 2H), 7.20 (m, 4H). ^{13}C {^{1}H} NMR (500 MHz, $CDCl_3$) **δ** (ppm) 15, 18.7, 40.5, 77.1, 124.9, 125.6, 128.3, 130.1, 133.7, 137.1, 170.7.

2-methyl-N-butyl-N-ethylbenzamide (**5b**) ^{1}H NMR (500 MHz, $CDCl_3$) **δ** (ppm) 0.7457 (t, J = 7.5, 1.5H), 0.9783 (t, J = 7.5, 1.5H), 1.0014 (t, J = 3.7, 1.5H), 1.0987 (s, J = 7.4, 1H), 1.2497 (t, J = 7.0, 1.5H), 1.4163 (m, 2H), 1.6588 (q, J = 7.9, 1H), 2.2742 (s, 1.5H), 2.2857 (s, 1.5H), 3.0404 (t, J = 7.15, 1H), 3.1112 (q, J = 6.45, 1H), 3.3763 (s, 1H), 3.7037 (s, 1H), 7.1706 (m, 4H). ^{13}C {^{1}H} NMR (500 MHz, $CDCl_3$) **δ** (ppm) 12.4061, 13.2428, 13.5024, 13.6178, 18.4071, 18.5514, 19.4169, 20.0517, 29.3418, 30.3804, 38.7185, 42.5845, 43.2770, 47.3450, 170.6120, 170.6419, 125.1014, 125.3033, 125.3437, 125.3841, 128.0896, 129.9371, 133.3998, 133.4906, 136.7716, 136.9836.

N-diethyl-2-[(trimethylsilyl)methyl] benzamide (**7a**) After adding compound (**5a**) (1.4712 g) to a dry round bottom flask, the flask was purged with dry N_2 gas whilst continuous stirring. Using a syringe, Et_2O (40 mL) was added followed by dry TMEDA (1.3 mL). The solution was the cooled with continuous stirring in an acetone-dry ice cooling bath, reaching a temperature of approximately -78 ℃. A $CH_3CHLiCH_2CH_3$ solution (6.0 mL) was added via a syringe and the reaction mixture was stirred at -78 ℃ for 15 minutes. To the resulting solution TMSCI (1.7 mL) was added by syringe moderately and mixture was promptly removed from cooling and allowed to warm to room temperature with stirring. The reaction mixture was sealed with parafilm and placed in a fume-hood for a week. Saturated NH_4Cl was added to the solution and warmed with stirring in a hot water bath. Air was blown into the solution to evaporate the saturated NH_4Cl prior to isolation of crude product. The solution was then extracted with $C_4H_8O_2$ (3 x 50 mL), with the organic layer then being washed with H_2O (50 mL) and ClH_2NaO_2 (2 x 50 mL). Following the extraction, the solution was dried (Na_2SO_4) and gravity filtered into dry flask. The solvent was subsequently removed on the rotovap in two batches and placed on a vacuum pump for 10 min. The crude product then underwent thin layer chromatography for product characterization, exhibiting a retention factor of 0.52. Compound (**7a**) was a yellow solution and a yield of 75.8 %. Since compound (**7a**) has been reported in literature before it has a CAS name and number of N,N-Diethyl-2[(trimethylsilyl)methyl]benzamide and 85370-87-2 respectively.[7]

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SUPPORTING INFORMATION

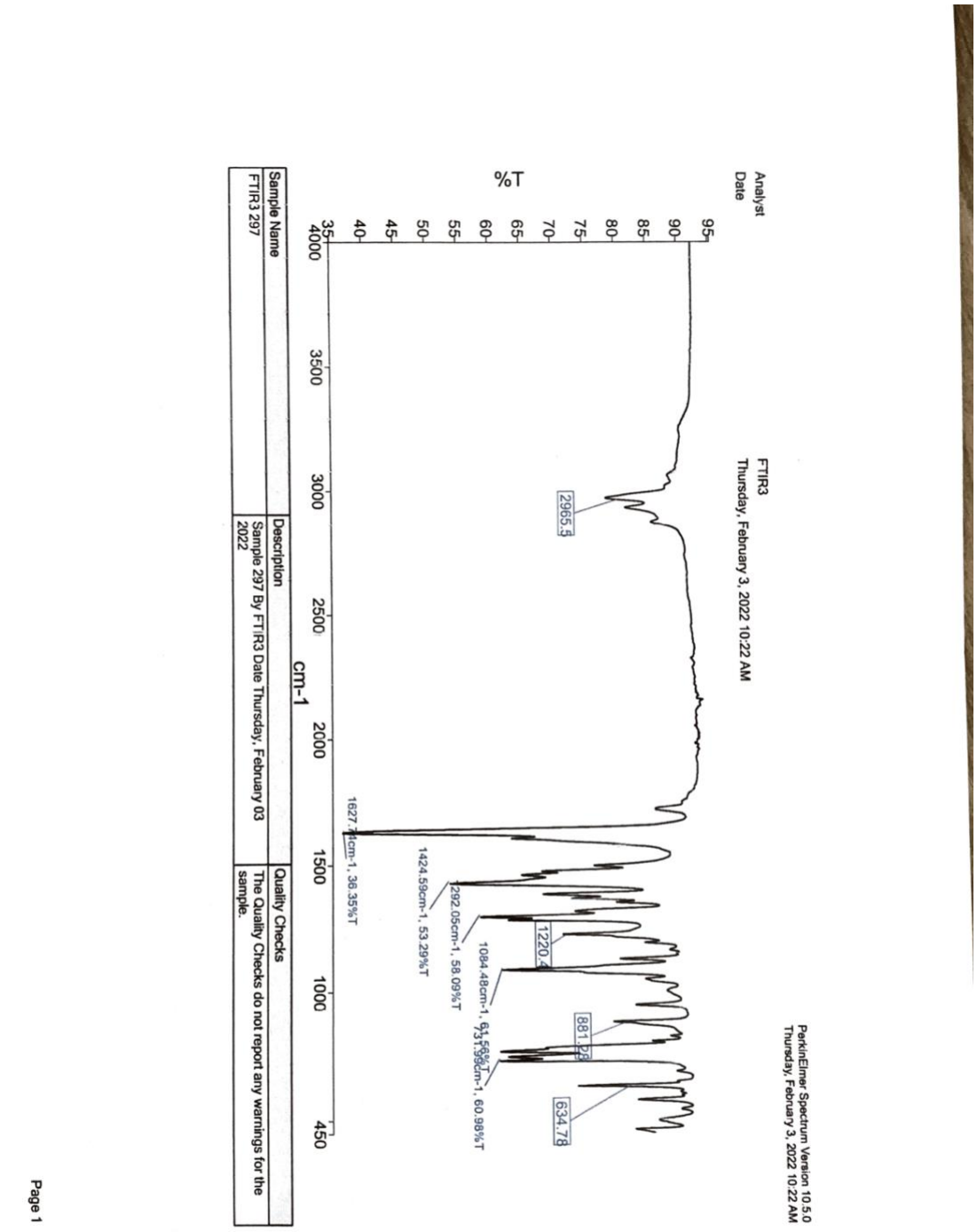

Figure. 1 IR spectra of N,N-diethyl-2-methylbenzamide (**5a**).

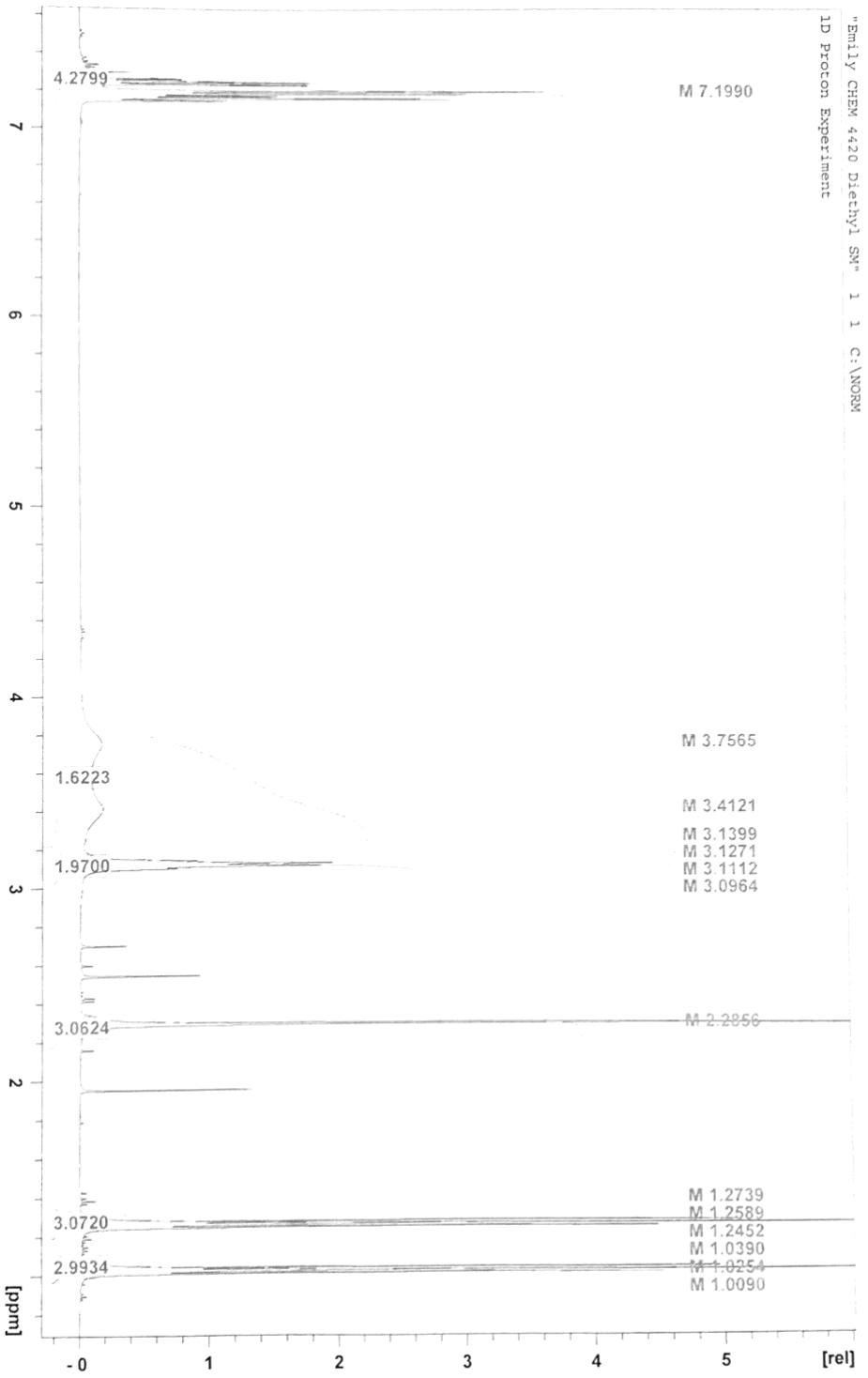

Figure. 2 ^{1}H NMR of N,N-diethyl-2-methylbenzamide (**5a**).

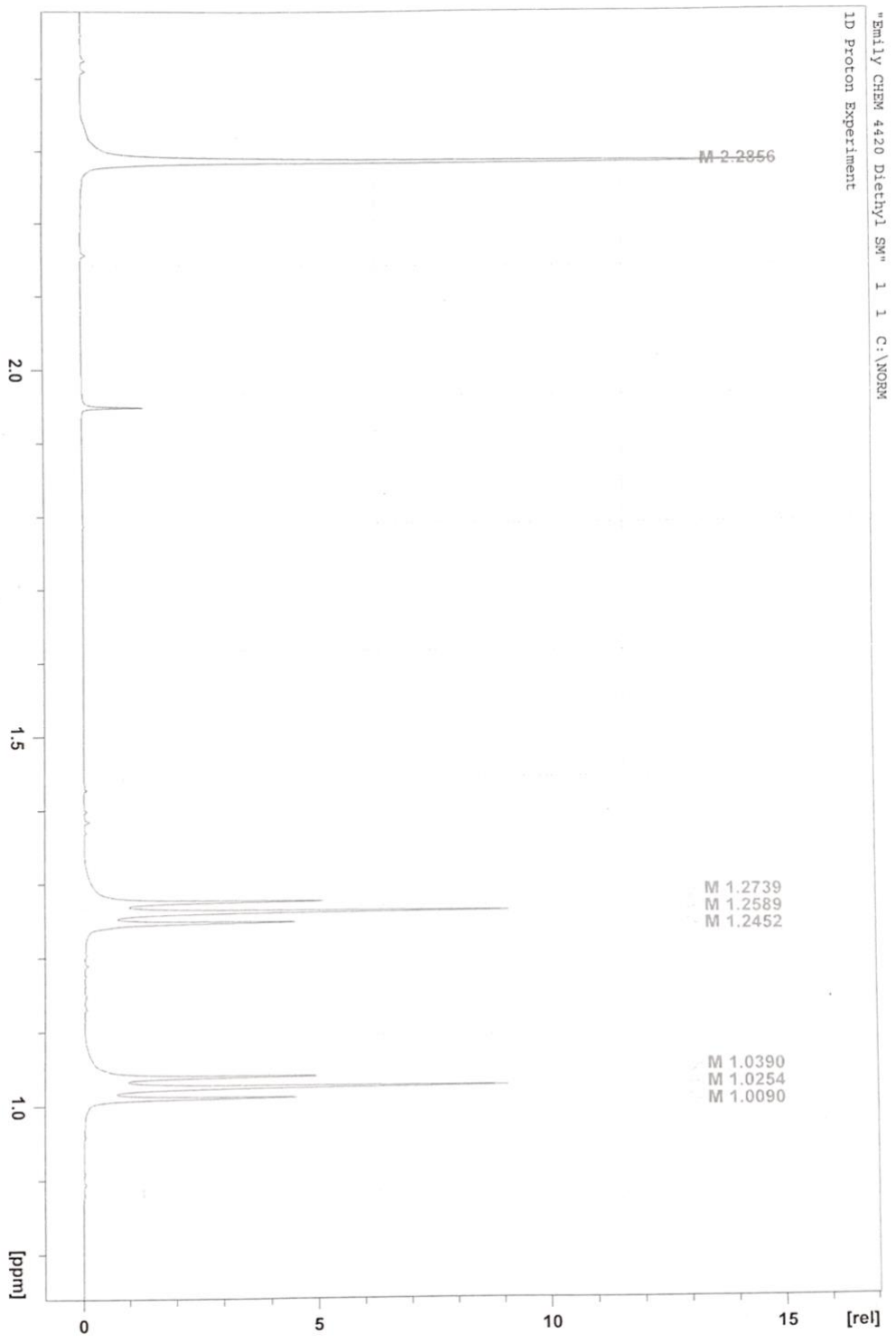

Figure. 3 ^{1}H NMR of N,N-diethyl-2-methylbenzamide (**5a**) with scale of 0.75 - 2.5 ppm.

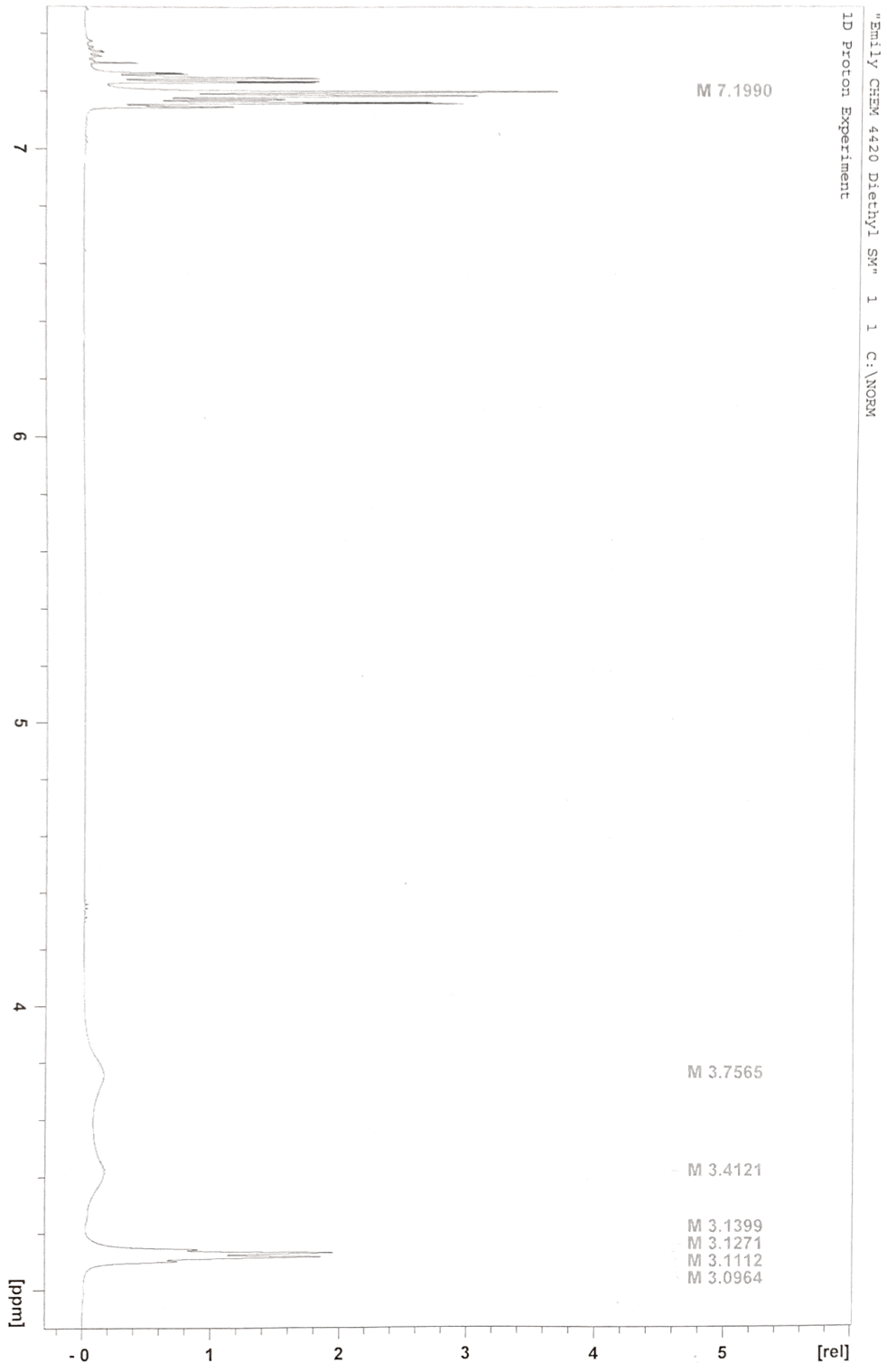

Figure. 4 ^{1}H NMR of N,N-diethyl-2-methylbenzamide (**5a**) with scale of 3 – 7.4 ppm.

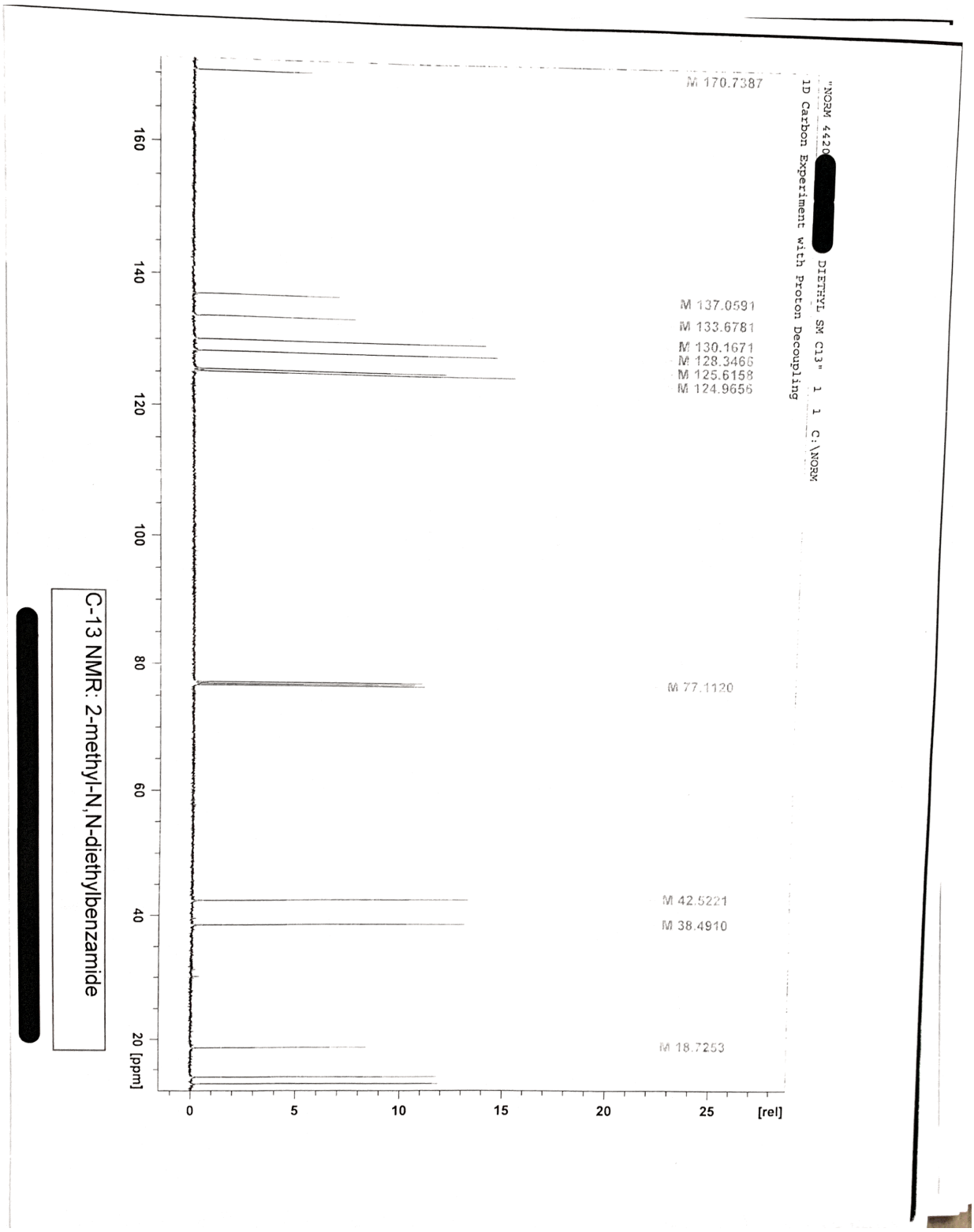

Figure. 5 ^{13}C NMR of N,N-diethyl-2-methylbenzamide (**5a**).

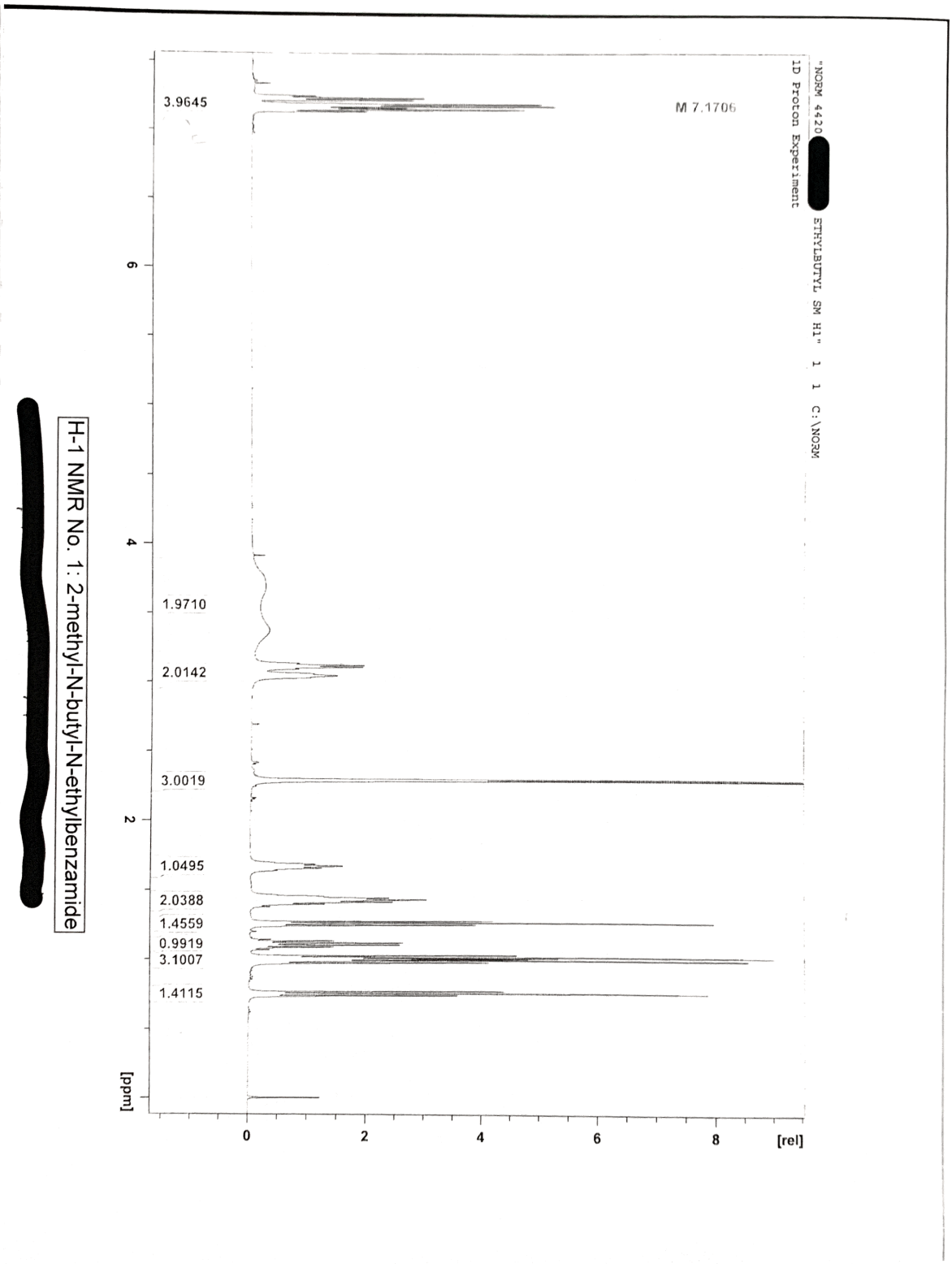

Figure. 6 ^{1}H NMR of 2-methyl-N-butyl-N-ethylbenzamide (**5b**).

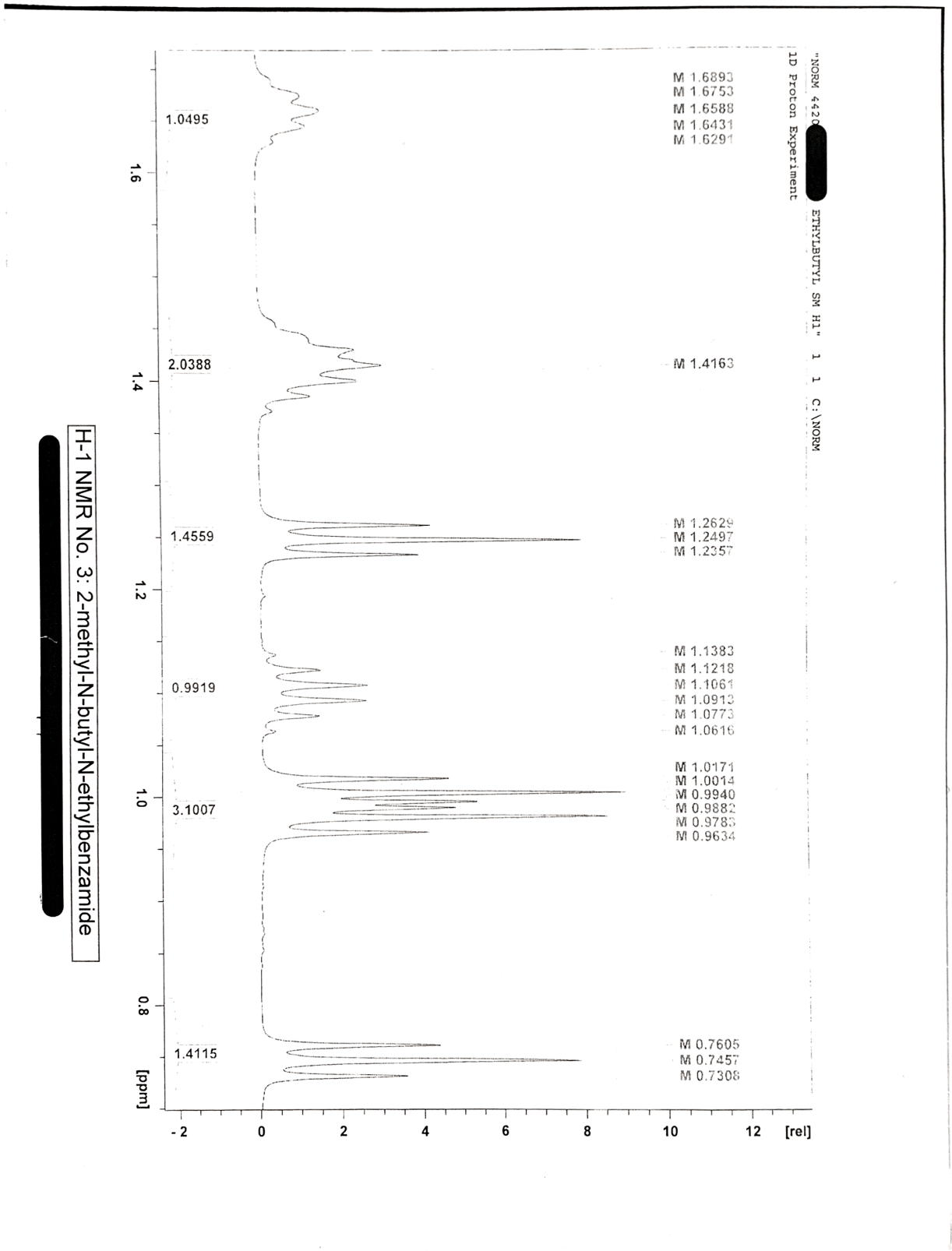

Figure. 7 ^{1}H NMR of 2-methyl-N-butyl-N-ethylbenzamide (**5b**) with scale of 0.7 – 1.7 ppm.

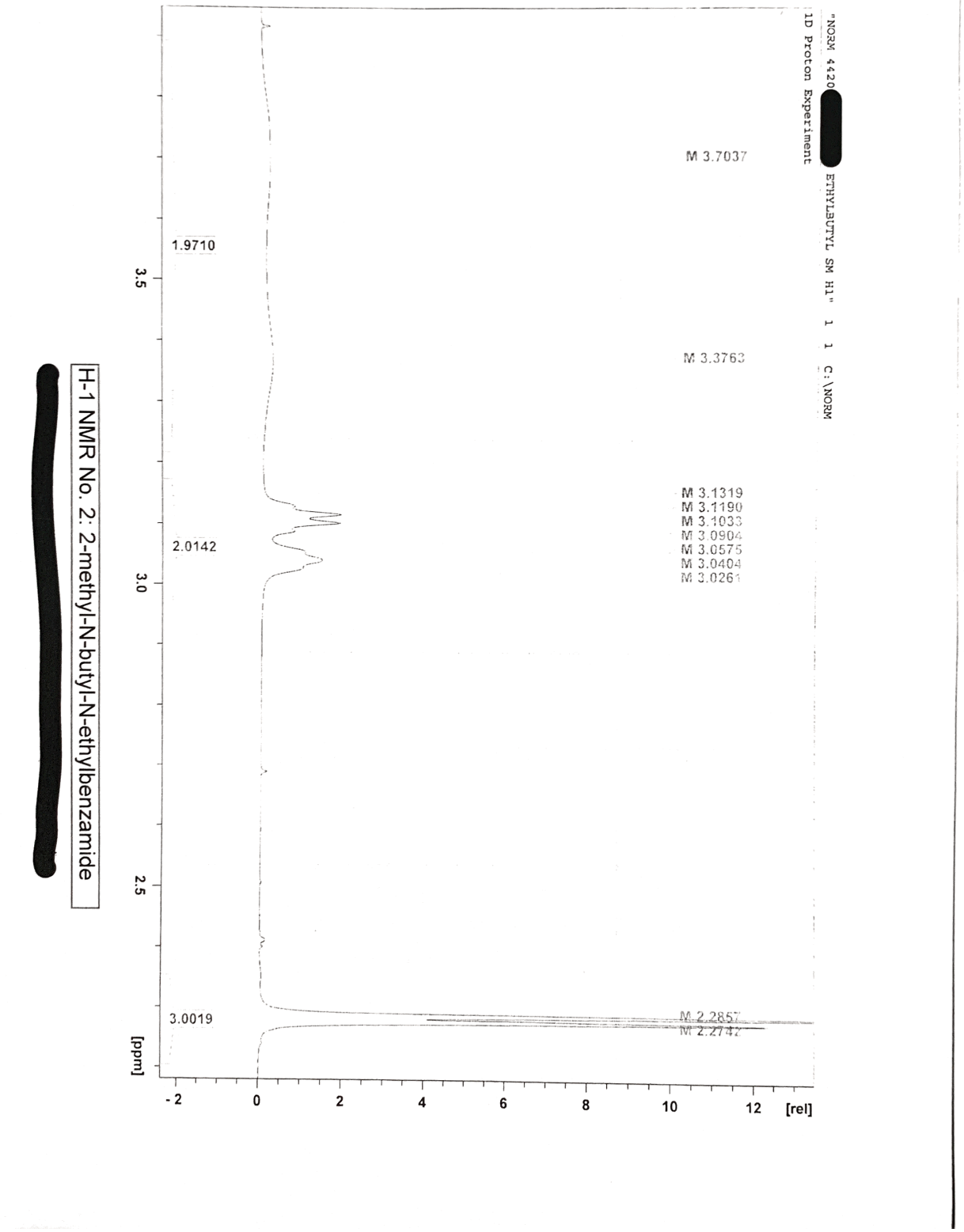

Figure. 8 ^{1}H NMR of 2-methyl-N-butyl-N-ethylbenzamide (**5b**) with scale of 2.2 – 3.9 ppm.

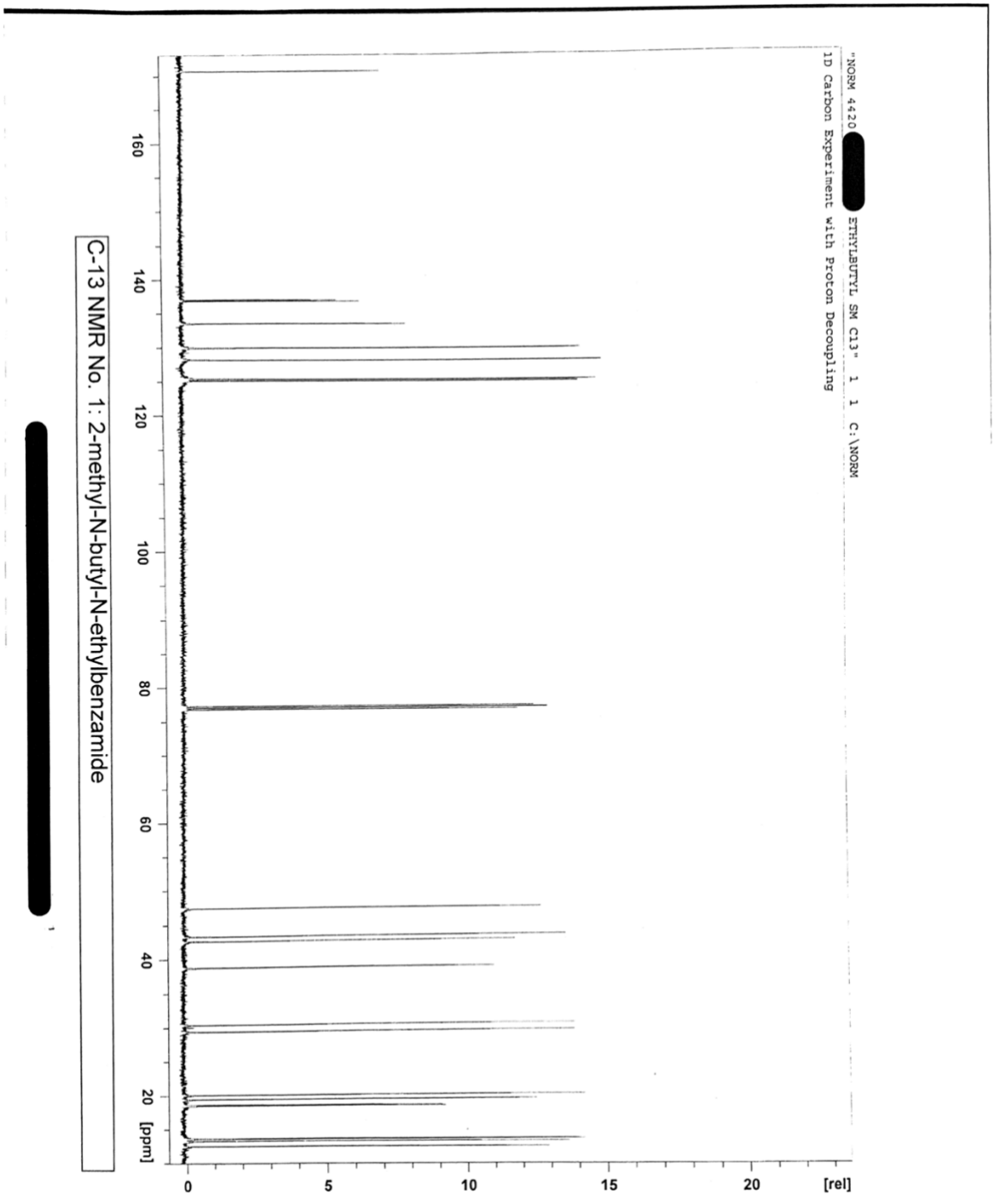

Figure. 9 ^{13}C NMR of 2-methyl-N-butyl-N-ethylbenzamide (**5b**).

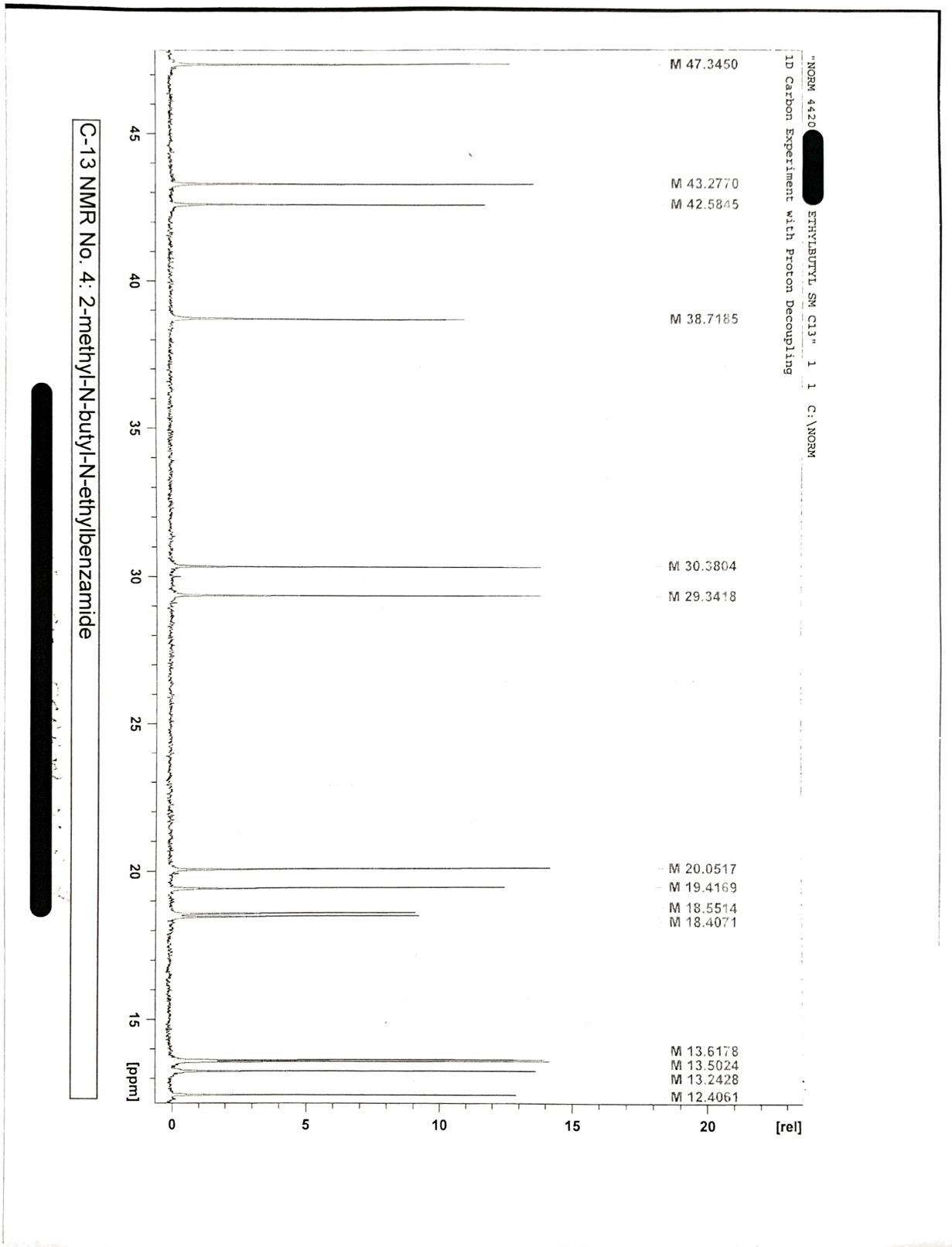

Figure. 10 ^{13}C NMR of 2-methyl-N-butyl-N-ethylbenzamide (**5b**) with scale of 12 – 48 ppm.

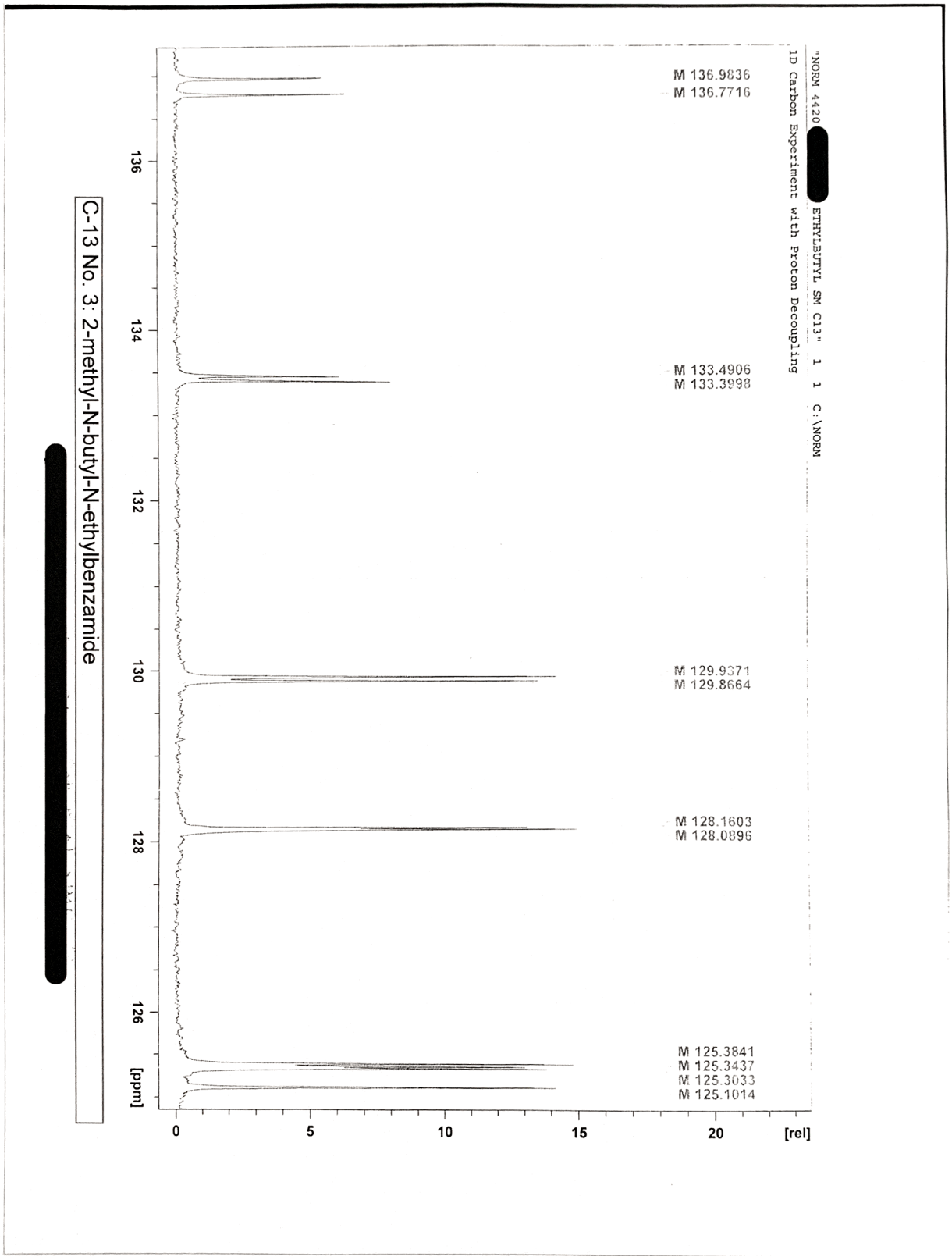

Figure. 11 ^{13}C NMR of 2-methyl-N-butyl-N-ethylbenzamide (**5b**) with scale of 125 - 137 ppm.

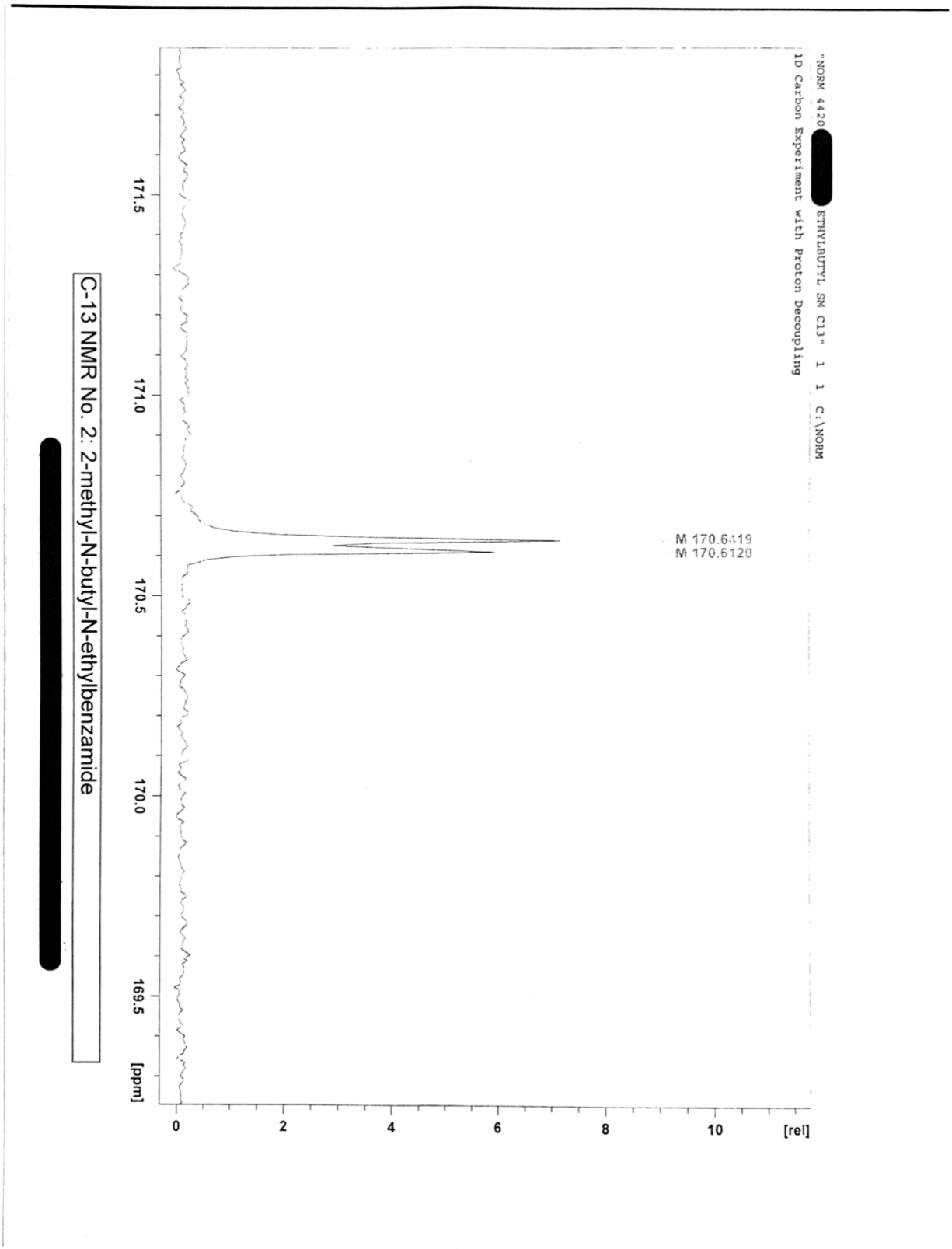

Figure. 12 ^{13}C NMR of 2-methyl-N-butyl-N-ethylbenzamide (**5b**) with scale of 169.3 – 171.8 ppm.