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Chemo-, Regio- and Diastereoselective Synthesis of Functionalized Cyclopropyl Nitriles by Cyclization of 1,1-Dianions with Epibromohydrin

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Supplementary Material

Experimental Procedure for the Synthesis of Cyclopropanes: To a THF solution (20 ml) of phenylacetonitrile (0.58 g, 5.00 mmol) was added *n*-BuLi (10.48 mmol, 4.23 ml, solution in *n*-hexane) at 0 °C. The solution was stirred for 1 h and subsequently a THF solution (20 ml) of $LiClO_4$ (0.34 g) and of epibromohydrin (0.33 g, 2.40 mmol) was added at −78 °C. The temperature was increased to −35 °C during 2 h and the solution was stirred at this temperature for 10 h. The solution was warmed to ambient during 1 h and stirred for 8 h. To the solution was added a saturated aqueous solution of NH_4Cl (40 ml) and ether (50 ml). The organic layer was separated and the aqueous layer was extracted with ether (2 x 50 ml) and dichloromethane (2 x 50 ml). The combined organic layers were extracted with a saturated aqueous solution of brine, dried (Na_2SO_4), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/ether = 4:1 → 1:1) to give **3a** as a colourless oil (330 mg, 79%, *Z*/*E* = 8:1). All compounds were prepared as racemic material and gave satisfactory spectroscopic and analytical and/ or high resolution mass data. The diastereomers of **3a-g** and **5** could not be separated. Compound **9** was formed as a single isomer. The diastereomers of **7** and **10** could be separated.

3a: Starting with phenylacetonitrile (0.58 g, 5.00 mmol), **3a** was isolated as a yellow oil (0.33 g, 79%, *E*/*Z* = 1:8). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.55 (m, 2 H, C*CH*$_2$CH), 1.91 (m, 1 H, CH), 3.34 (br, 1 H, OH), 3.76 (dd, *J* = 12 Hz, *J* = 5 Hz, 1 H, *CH*$_2$OH), 3.98 (dd, *J* = 12 Hz, *J* = 5 Hz, 1 H, *CH*$_2$OH), 7.28 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 16.08 (CN), 21.23 (CH_2), 31.30 (CH), 62.62 (CH_2OH), 120.57 (C), 125.82, 127.56, 128.73 (CH-Ph), 135.52 (C). MS (EI, 70 eV): 173 (M^+, 18), 143 (24), 129 (100), 115 (26), 103 (34); the exact molecular mass *m*/*z* = 173.0841±2 mD (M^+) for $C_{11}H_{11}NO$ was confirmed by HRMS (EI, 70 eV). Anal.: Calcd. for $C_{11}H_{11}NO$: C 76.28, H 6.40; found: C 76.46, H 6.28.

3b: Starting with *p*-tolylacetonitrile (0.65 g, 5.00 mmol), **3b** was isolated as a colorless oil (0.548 g, 56%, *E/Z* = 1:7). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.55 (m, 2 H, CCH_2CH), 1.92 (m, 1 H, CH), 2.33 (s, 3 H, CH_3), 3.14 (dd, *J* = 12 Hz, *J* = 9 Hz, 1 H, CH_2OH, *E*-diastereomer), 3.46 (dd, *J* = 12 Hz, *J* = 5 Hz, 1 H, CH_2OH, *E*-diastereomer), 3.78 (dd, *J* = 12 Hz, *J* = 8 Hz, 1 H, CH_2OH, *Z*-diastereomer), 4.04 (dd, *J* = 12 Hz, *J* = 6 Hz, 1 H, CH_2OH, *Z*-diastereomer), 7.19 (m, 4 H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 16.02 (CN), 20.91 (CH_3), 21.08 (CCH_2CH), 31.17 (CH), 62.99 (CH_2OH), 120.88 (C), 126.04, 129.52 (CH, Ar), 132.63, 137.62 (C, Ar). MS (EI, 70 eV): 187 (M^+, 12), 157 (32), 143 (100), 115 (16); the exact molecular mass *m/z* = 187.0997±2 mD (M^+) for $C_{12}H_{13}NO$ was confirmed by HRMS (EI, 70 eV).

3c: Starting with *p*-methoxyphenylacetonitrile (0.73 g, 5.00 mmol), **3c** was isolated as a colorless oil (0.48 g, 52%, *E/Z* = 1:7). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.52 (m, 2 H, CCH_2CH), 1.86 (m, 1 H, CH), 2.37 (br, 1 H, OH), 3.14 (dd, *J* = 12 Hz, *J* = 9 Hz, 1 H, CH_2OH, *E*-diastereomer), 3.45 (dd, *J* = 12 Hz, *J* = 5 Hz, 1 H, CH_2OH , *E*-diastereomer), 3.77 (dd, *J* = 12 Hz, *J* = 8 Hz, 1 H, CH_2OH , *Z*-diastereomer), 3.78 (s, 3 H, CH_3), 4.05 (dd, *J* = 12 Hz, *J* = 5 Hz, 1 H, CH_2OH , *Z*-diastereomer), 6.84 (m, 2 H, Ar), 7.23 (m, 2 H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, *Z*-diastereomer): δ = 16.23 (CN), 20.72 (CCH_2CH), 30.79 (CH), 55.30 (CH_3), 63.03 (CH_2OH), 114.25 (CH, Ar), 121.06 (C), 127.61 (C, Ar), 127.86 (CH, Ar), 159.17 (C, Ar). MS (EI, 70 eV): 203 (M^+, 32), 173 (57), 159 (100), 116 (11); the exact molecular mass *m/z* = 203.0946±2 mD (M^+) for $C_{12}H_{13}NO_2$ was confirmed by HRMS (EI, 70 eV).

3d: Starting with *m*-tolylacetonitrile (0.65 g, 5.00 mmol), **3d** was isolated as a yellow oil (0.32 g, 71%, *E/Z* = 1:7). ^{1}H NMR ($CDCl_3$, 250 MHz, *Z*-isomer): δ = 1.59 (m, 2 H, C*CH*$_2$CH), 1.95 (m, 1 H, CH), 2.34 (s, 3 H, CH_3), 3.79 (dd, *J* = 12 Hz, *J* = 8 Hz, 1 H, *CH*$_2$OH), 4.06 (dd, *J* = 12 Hz, *J* = 5 Hz, 1 H, *CH*$_2$OH), 7.18 (m, 4 H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, *Z*-isomer): δ = 16.04 (CN), 21.22 (C*CH*$_2$CH), 21.32 (CH_3), 31.35 (CH), 63.05 (CH_2OH), 120.82 (C), 122.92, 126.88, 128.53, 128.79 (CH, Ar), 135.52, 138.74 (C, Ar). MS (EI, 70 eV): 187 (M^+, 25), 143 (100), 142 (13), 115 (17); the exact molecular mass *m/z* = 187.0997±2 mD (M^+) for $C_{12}H_{13}NO$ was confirmed by HRMS (EI, 70 eV).

3e: Starting with *m*-methoxyphenylacetonitrile (0.73 g, 5.00 mmol), **3e** was isolated as a yellow oil (0.36 g, 75%, *E/Z* = 1:6). ^{1}H NMR ($CDCl_3$, 250 MHz, *Z*-isomer): δ = 1.59 (m, 2 H, C*CH*$_2$CH), 1.91 (m, 1 H, CH), 2.33 (br, 1 H, OH), 3.80 (s, 3 H, CH_3) 3.81 (dd, *J* = 12 Hz, *J* = 8 Hz, 1 H, *CH*$_2$OH), 4.05 (dd, *J* = 12 Hz, *J* = 5 Hz, 1 H, *CH*$_2$OH), 6.85 (m, 3 H, Ar), 7.25 (m, 1 H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, *Z*-isomer): δ = 16.11 (CN), 21.41 (C*CH*$_2$CH), 31.57 (CH), 55.32 (CH_3), 63.09 (CH_2OH), 112.10, 113.09, 118.10 (CH, Ar), 120.63 (C), 130.01 (CH, Ar), 137.22, 159.97 (CH, Ar). MS (EI, 70 eV): 203 (M^+, 18), 173 (12), 159 (100); the exact molecular mass *m/z* = 203.0946±2 mD (M^+) for $C_{12}H_{13}NO_2$ was confirmed by HRMS (EI, 70 eV).

3f: Starting with *o*-tolylacetonitrile (0.65 g, 5.00 mmol), **3f** was isolated as a colorless oil (0.15 g, 34%, *E/Z* = 1:5). ^{1}H NMR ($CDCl_3$, 250 MHz, *Z*-isomer): δ = 1.50 (m, 2 H, C*CH*$_2$CH), 1.82 (m, 1 H, CH), 2.54 (CH_3), 3.84 (dd, *J* = 12 Hz, *J* = 8 Hz, 1 H, *CH*$_2$OH), 4.12 (dd, *J* = 12 Hz, *J* = 5 Hz, 1 H, *CH*$_2$OH), 7.22 (m, 4 H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, *Z*-isomer): δ = 16.96 (CN), 19.28 (C*CH*$_2$CH), 19.40 (CH), 29.04 (CH_3), 63.04 (CH_2OH), 120.60 (C), 126.28, 128.79, 129.55, 130.72 (CH-Ar), 133.53, 138.80 (C). MS (EI, 70 eV): 187 (M^+,

16), 157 (18), 143 (100), 115 (34); the exact molecular mass *m/z* = 187.0997±2 mD (M^+) for $C_{12}H_{13}NO$ was confirmed by HRMS (EI, 70 eV).

3g: Starting with naphthylacetonitrile (0.83 g, 5.00 mmol), **3g** was isolated as a yellow oil (0.43 g, 81%, *E/Z* = 1:5). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.69 (m, 2 H, C*CH*$_2$CH, *Z*-diastereomer), 1.82 (m, 2 H, C*CH*$_2$CH, *E*-diastereomer), 2.06 (m, 1 H, CH, *Z*-diastereomer), 2.22 (m, 1 H, CH, *E*-diastereomer), 2.47 (br, 1 H, OH), 3.13 (dd, *J* = 12 Hz, *J* = 8 Hz, 1 H, *CH*$_2$OH, *E*-diastereomer), 3.49 (dd, *J* = 12 Hz, *J* = 6 Hz, 1 H, *CH*$_2$*OH*, *E*-diastereomer), 3.84 (dd, *J* = 12 Hz, *J* = 9 Hz, 1 H, *CH*$_2$OH, *Z*-diastereomer), 4.12 (dd, *J* = 12 Hz, *J* = 5 Hz, 1 H, *CH*$_2$OH, *Z*-diastereomer), 7.35 (m, 1 H, Ar), 7.51 (m, 2 H, Ar), 7.82 (m, 4 H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 16.43 (CN), 21.51 (C*CH*$_2$CH), 31.69 (CH), 63.35 (*CH*$_2$OH), 121.08 (C), 123.72, 125.73, 126.70, 127.04, 127.88, 127.99, 129.21 (CH, Ar), 132.85, 133.15, 133.34 (C-Ar). MS (EI, 70 eV): 223 (M^+, 31), 193 (37), 179 (100), 165 (35); the exact molecular mass *m/z* = 223.0997±2 mD (M^+) for $C_{15}H_{13}NO$ was confirmed by HRMS (EI, 70 eV).

5: Starting with *N*-methylpyrrolylacetonitrile (0.60 g, 5.00 mmol), **5** was isolated as a yellow oil (0.35 g, 83%, *E/Z* = 1:3). ^{1}H NMR ($CDCl_3$, 250 MHz, *Z*-isomer): δ = 1.48 (m, 1 H, C*CH*$_2$CH), 1.59 (m, 1 H, C*CH*$_2$CH), 1.84 (m, 1 H, CH), 3.71 (m, 1 H, *CH*$_2$OH), 3.78 (s, 3 H, CH_3), 4.16 (dd, *J* = 12 Hz, *J* = 5 Hz, 1 H, *CH*$_2$OH), 6.03 (m, 2 H, Hetar), 6.61 (m, 1 H, Hetar). ^{13}C NMR ($CDCl_3$, 75 MHz, *Z*-isomer): δ = 11.52 (CN), 19.37 (C*CH*$_2$CH), 29.69 (CH), 34.02 (CH_3), 62.82 (CH_2OH), 106.98, 109.19 (CH, Hetar), 120.03 (C), 123.53 (CH, Hetar), 126.31 (C, Hetar). MS (EI, 70 eV): 176 (M^+, 44), 145 (100), 132 (54), 118 (15); the exact molecular mass *m/z* = 176.0950±2 mD (M^+) for $C_{10}H_{12}N_2O$ was confirmed by HRMS (EI, 70 eV).

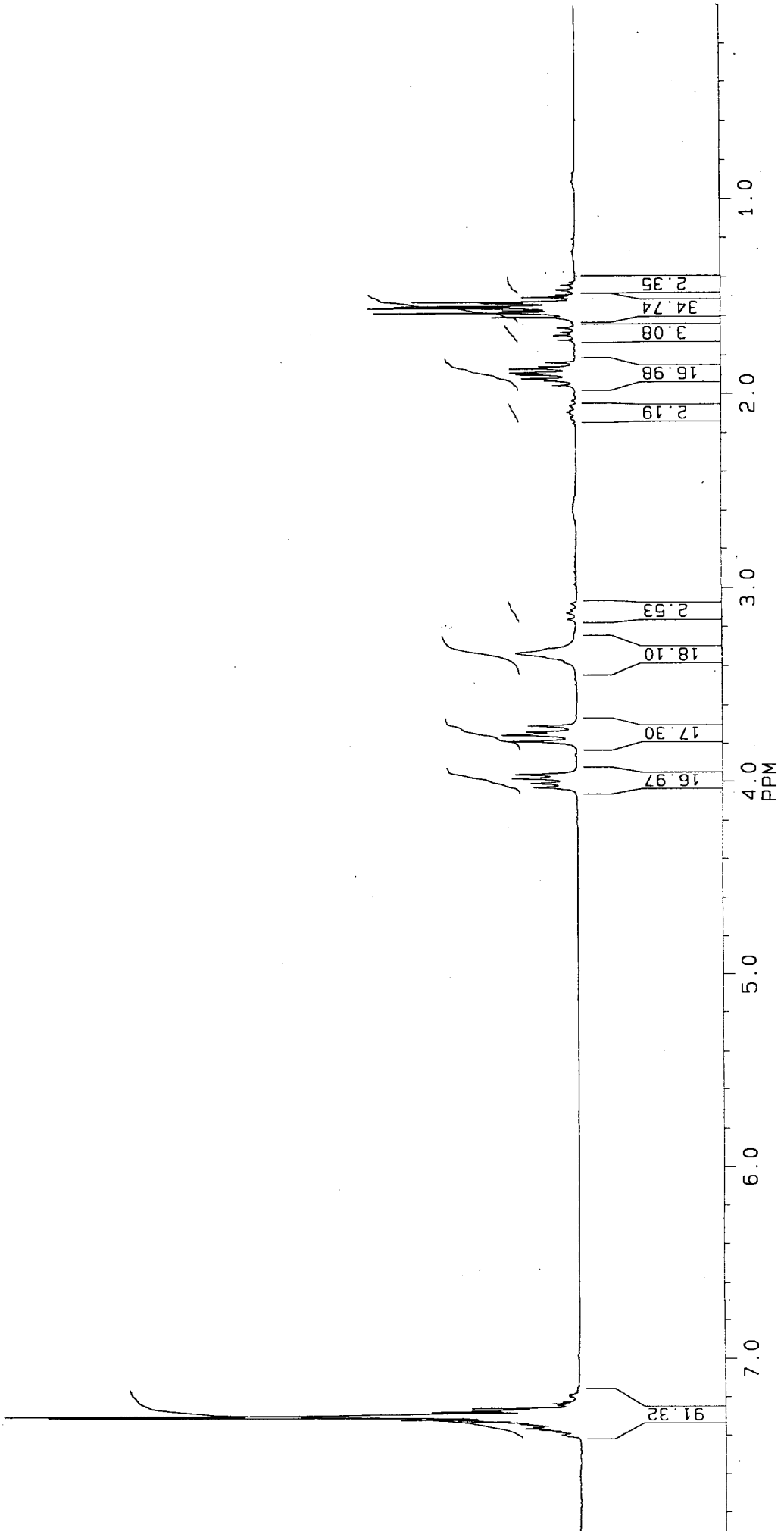
7: Starting with 2-thienylacetonitrile (0.61 g, 5.00 mmol), **7** was isolated in two fractions as yellow oils (fraction A: **7a**: 168 mg, 39%, *E/Z* < 2:98; fraction B: **7a** + **7b**: 182 mg, 43%, *E/Z* = 1:4; combined yield of fractions A + B: 350 mg, 82%, *E/Z* = 1:9). ^{1}H NMR ($CDCl_3$, 250 MHz): **7a**: δ = 1.60 (d, *J* = 7 Hz, 2 H, C*CH*$_2$CH), 1.98 (m, 1 H, CH), 3.02 (br, 1 H, OH), 3.74 (dd, *J* = 12 Hz, *J* = 8 Hz, 1 H, *CH*$_2$OH), 4.00 (dd, *J* = 12 Hz, *J* = 5 Hz, 1 H, *CH*$_2$OH), 6.91 (dd, *J* = 5 Hz, *J* = 4 Hz, 1 H, Ar), 7.04 (dd, *J* = 3 Hz, *J* = 1 Hz, 1 H, Ar), 7.15 (dd, *J* = 5 Hz, *J* = 1 Hz, 1 H, Ar). **7b**: δ = 1.48 (m, 1 H, C*CH*$_2$CH), 1.84 (m, 1 H, C*CH*$_2$CH), 2.16 (m, 1 H, CH), 2.74 (br, 1 H, OH), 3.26 (dd, *J* = 12 Hz, *J* = 8 Hz, 1 H, *CH*$_2$OH), 3.59 (dd, *J* = 12 Hz, *J* = 5 Hz, 1 H, *CH*$_2$OH), 6.97 (dd, *J* = 5 Hz, *J* = 4 Hz, 1 H, Ar), 7.09 (dd, *J* = 3 Hz, *J* = 2 Hz, 1 H, Ar), 7.28 (dd, *J* = 5 Hz, *J* = 1 Hz, 1 H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, **7a**): δ = 15.02 (CN), 22.70 (C*CH*$_2$CH), 32.52 (CH), 62.24 (*CH*$_2$OH), 119.87 (C), 124.74, 125.91, 127.02 (CH, Ar), 139.56 (C). MS (EI, 70 eV): 179 (M^+, 18), 149 (27), 135 (100); the exact molecular mass *m/z* = 179.0405±2 mD (M^+) for C_9H_9SNO was confirmed by HRMS (EI, 70 eV).

9: Starting with trimethylsilylacetonitrile (0.56 g, 5.00 mmol), **9** was isolated as a colorless oil (0.26 g, 65%, *E/Z* > 98:2). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.13 (s, 9 H, $SiMe_3$), 1.06 (dd, *J* = 8 Hz, *J* = 5 Hz, 1 H, C*CH*$_2$CH), 1.15 (dd, *J* = 8 Hz, *J* = 5 Hz, 1 H, C*CH*$_2$CH), 1.46 (m, 1 H, CH), 2.16 (br, 1 H, OH), 3.68 (dd, *J* = 12 Hz, *J* = 7 Hz, 1 H, *CH*$_2$OH), 3.93 (dd, *J* = 12 Hz, *J* = 6 Hz, 1 H, *CH*$_2$OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −3.57 ($Si(CH_3)_3$), 1.03 (CN), 15.64 (C*CH*$_2$CH), 24.44 (CH), 63.74 (CH_2OH), 122.41 (C). MS (DCI, NH_3): 204 ($[M+18+17]^+$,13), 187 ($[M+18]^+$, 100), 170 ($[M+1]^+$, 11).

Synthesis of Cyclopropane 10: To a THF suspension (15 mL) of NaH (99 mg, 4.2 mmol) was added **9** (303 mg, 1.79 mmol) at 0 °C and the mixture was stirred for 30 min. Benzylic bromide (370 mg, 2.15 mmol) was added, the mixture was warmed to ambient and stirred for

2 d. An aqueous solution of Na_2CO_3 (50 mL, 10%) and ether were added, the organic and the aqueous layer were separated. The latter was extracted with ether (3 x 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and the filtrate was cncentrated *in vacuo*. The residue was purified by chromatgraphy (silica gel, ether/petroleum ether = 1:20 → 1:1) to give **10** as a yellow oil (235 mg, 70%, *E/Z* = 1:1). The diastereomers were separated by chromatography to give the pure *E*-diastereomer **10a** (106 mg, 32%) and the *Z*-diastereomer **10b** (97 mg, 29%). The isomers were assigned by NOESY experiments. ^{1}H NMR ($CDCl_3$, 250 MHz): **10a**: δ = 1.07 (m, 1 H, NCCH), 1.23 (m, 1 H, CH*CH*$_2$CH), 1.36 (m, 1 H, CH*CH*$_2$CH), 1.79 (m, 1 H, CH), 3.19 (dd, *J* = 12 Hz, *J* = 6 Hz, 1 H, *CH*$_2$OBn), 3.52 (dd, *J* = 12 Hz, *J* = 5 Hz, 1 H, *CH*$_2$OBn), 4.54 (s, 2 H, *CH*$_2$Ph), 7.33 (m, 5 H, Ph). **10b**: δ = 0.99 (m, 1 H, CH*CH*$_2$CH), 1.27 (m, 1 H, CH*CH*$_2$CH), 1.61 (m, 2 x 1 H, 2 x CH), 3.53 (dd, *J* = 12 Hz, *J* = 8 Hz, 1 H, *CH*$_2$OBn), 3.75 (dd, *J* = 12 Hz, *J* = 5 Hz, 1 H, *CH*$_2$OBz), 4.59 (s, 2 H, *CH*$_2$Ph), 7.19 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz): **10b**: δ = 0.98 (CH), 11.27 (CN), 20.51 (CH), 69.41, 72.86 (CH_2), 121.36 (C), 127.58, 127.83, 128.44 (CH-Ar), 137.57 (C-Ar). MS (EI, 70 eV): 187 (M^+, 10), 91 (100), 79.1 (8); the exact molecular mass *m/z* = 187.0997±2 mD (M^+) for $C_{12}H_{13}NO$ was confirmed by HRMS (EI, 70 eV).

3a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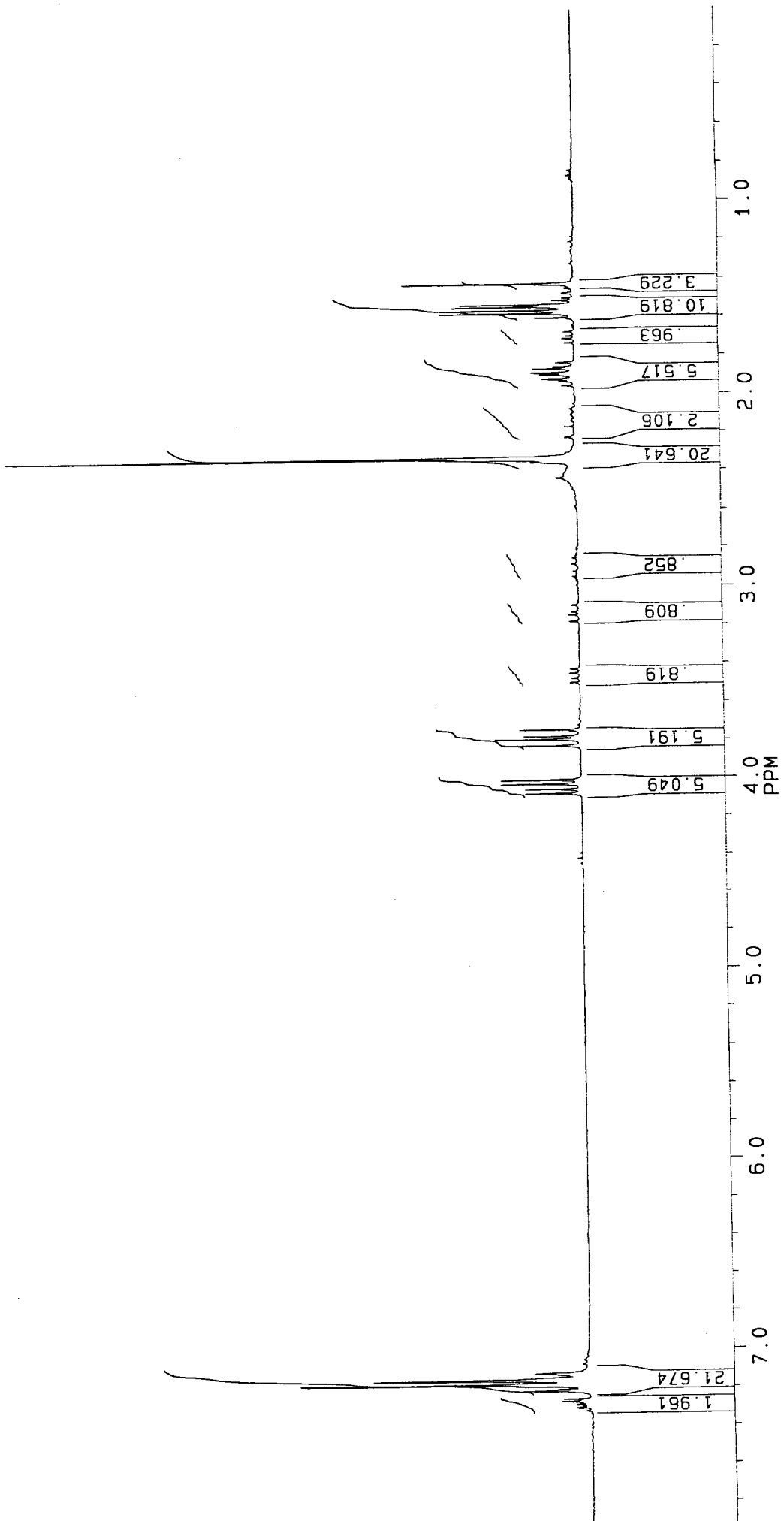

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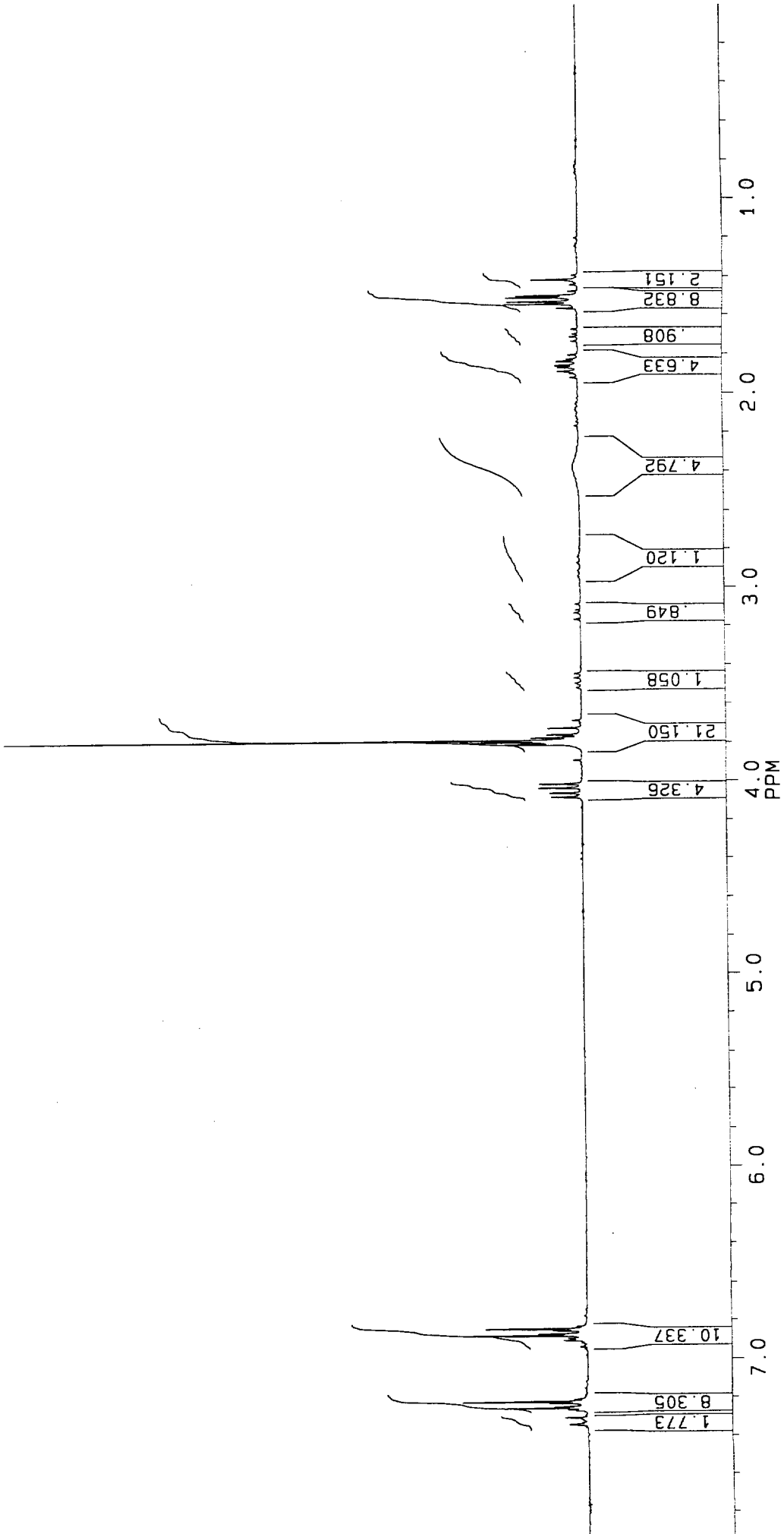

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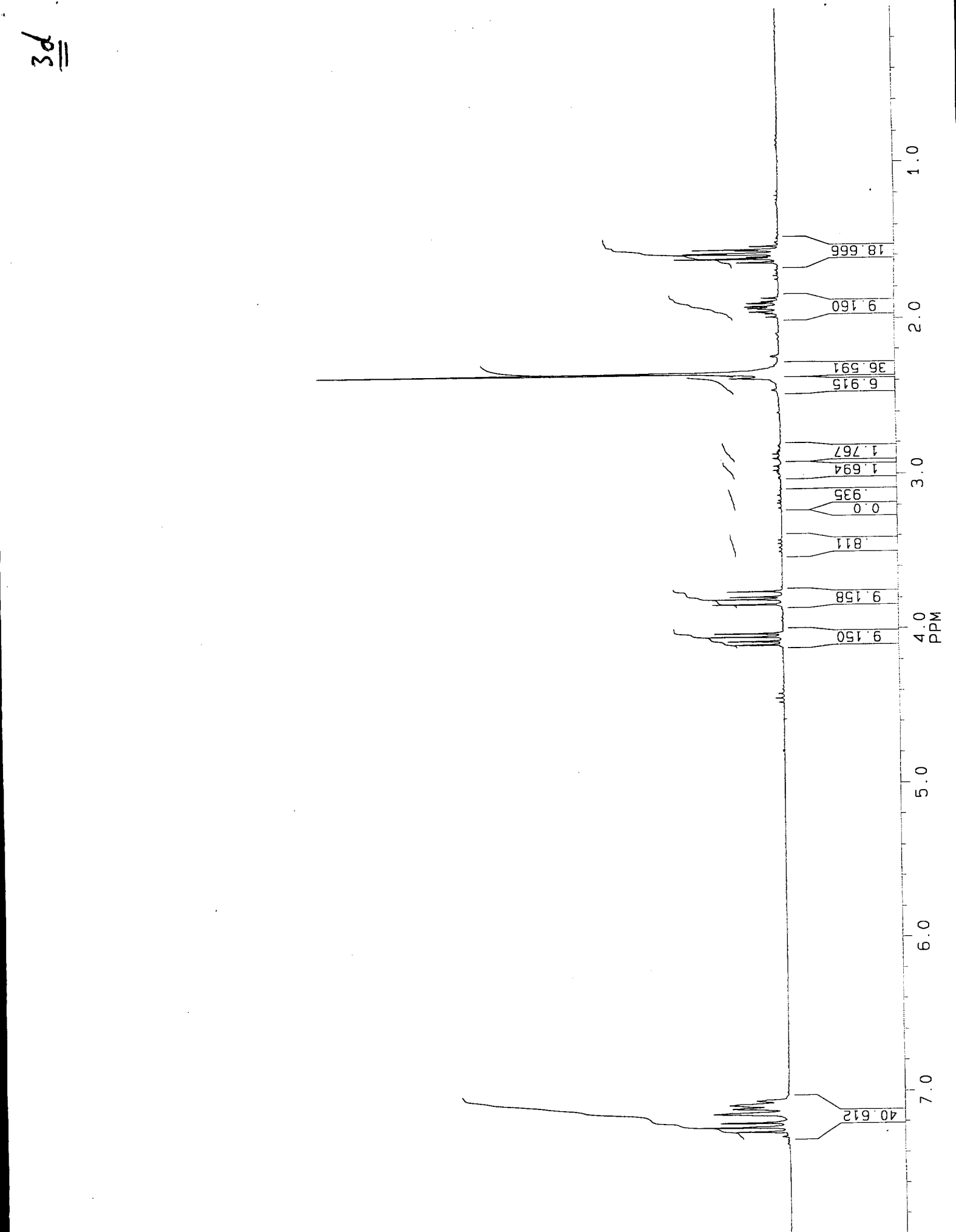
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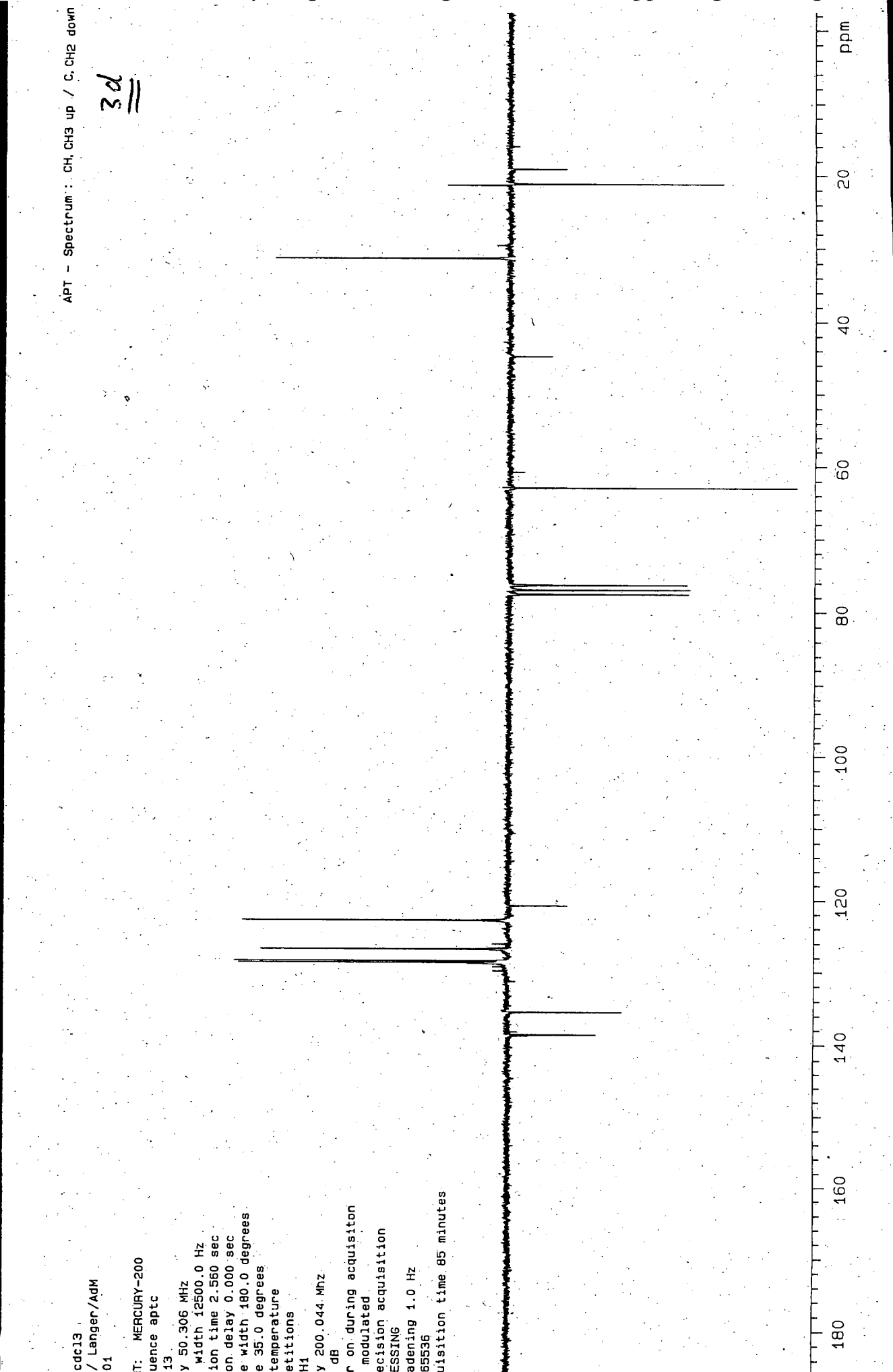

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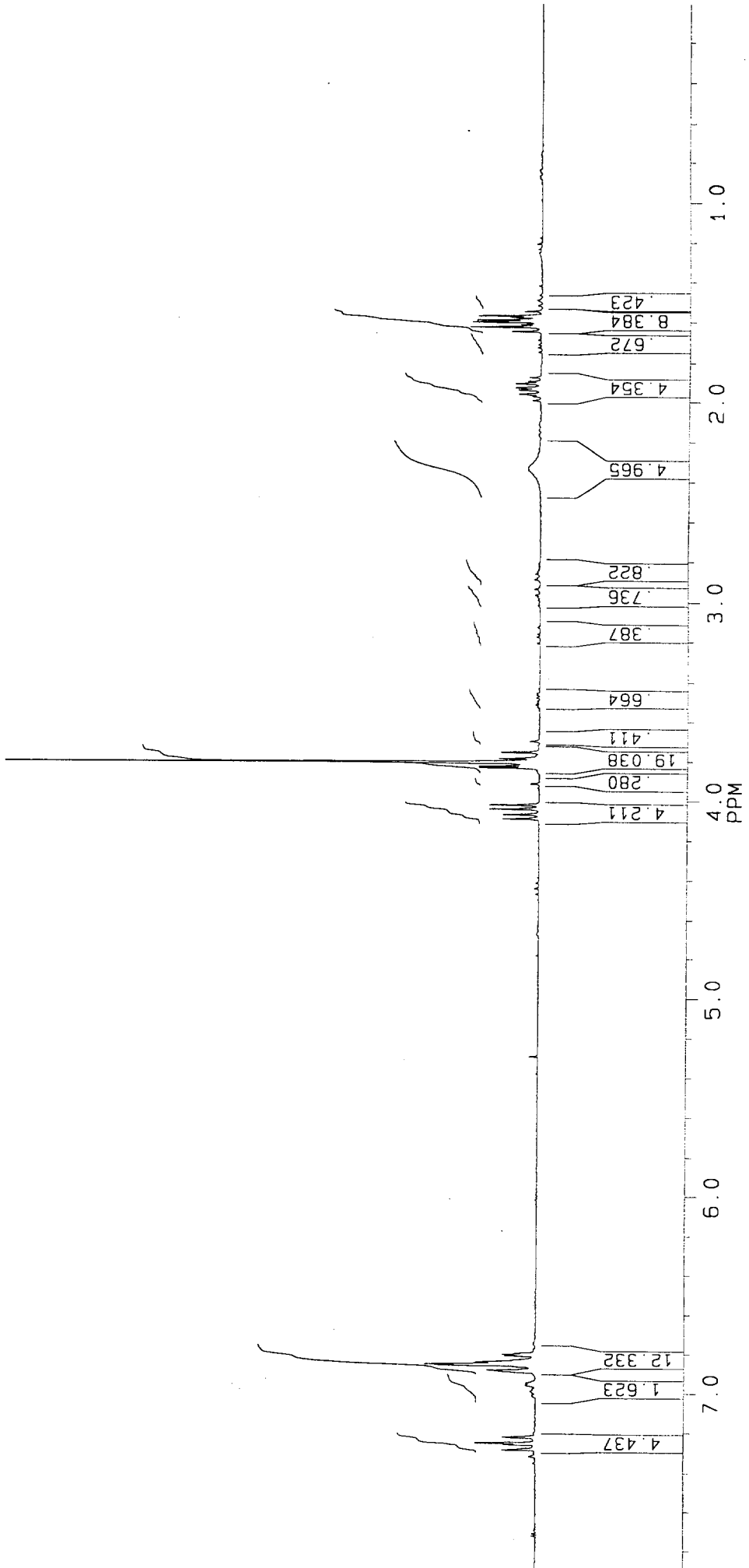

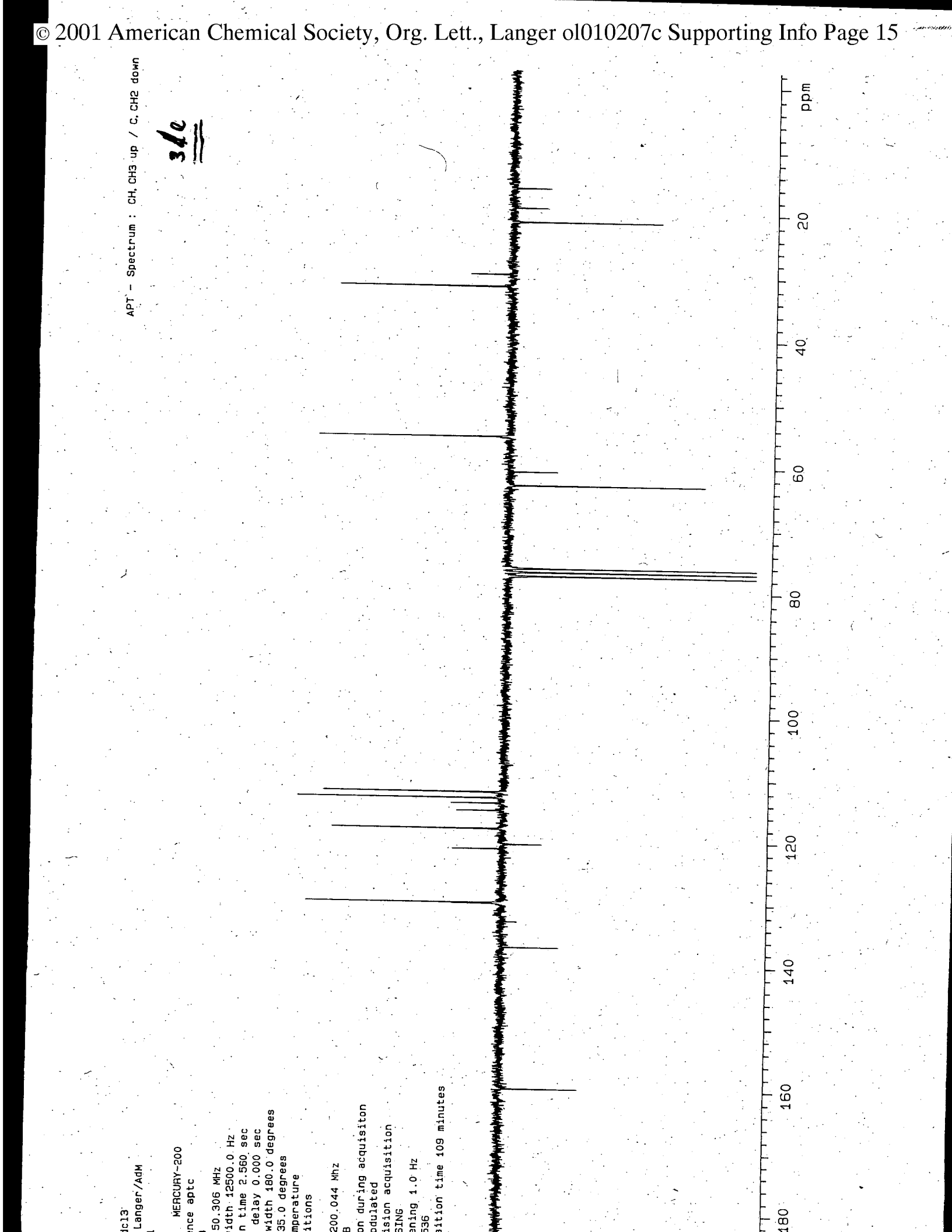

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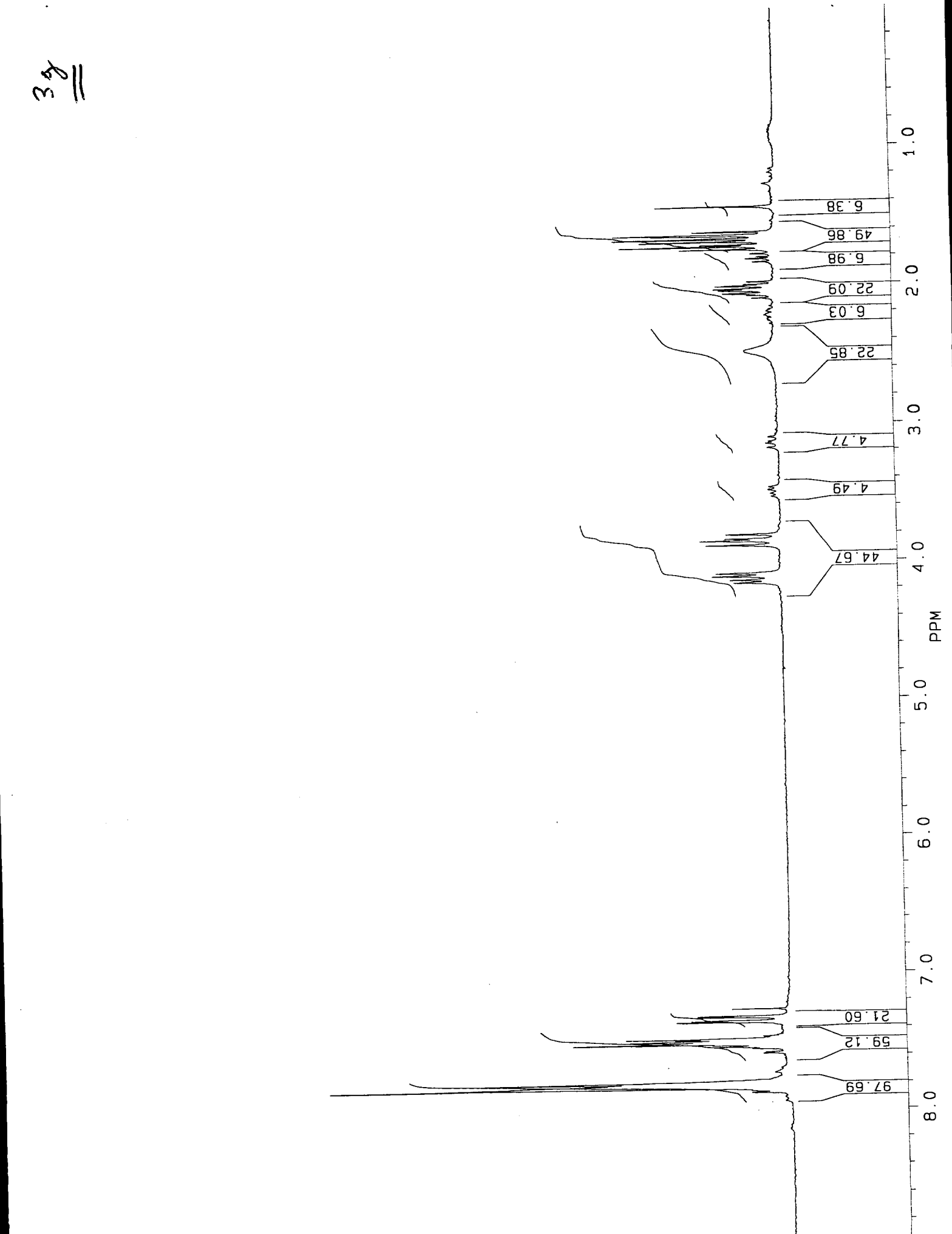

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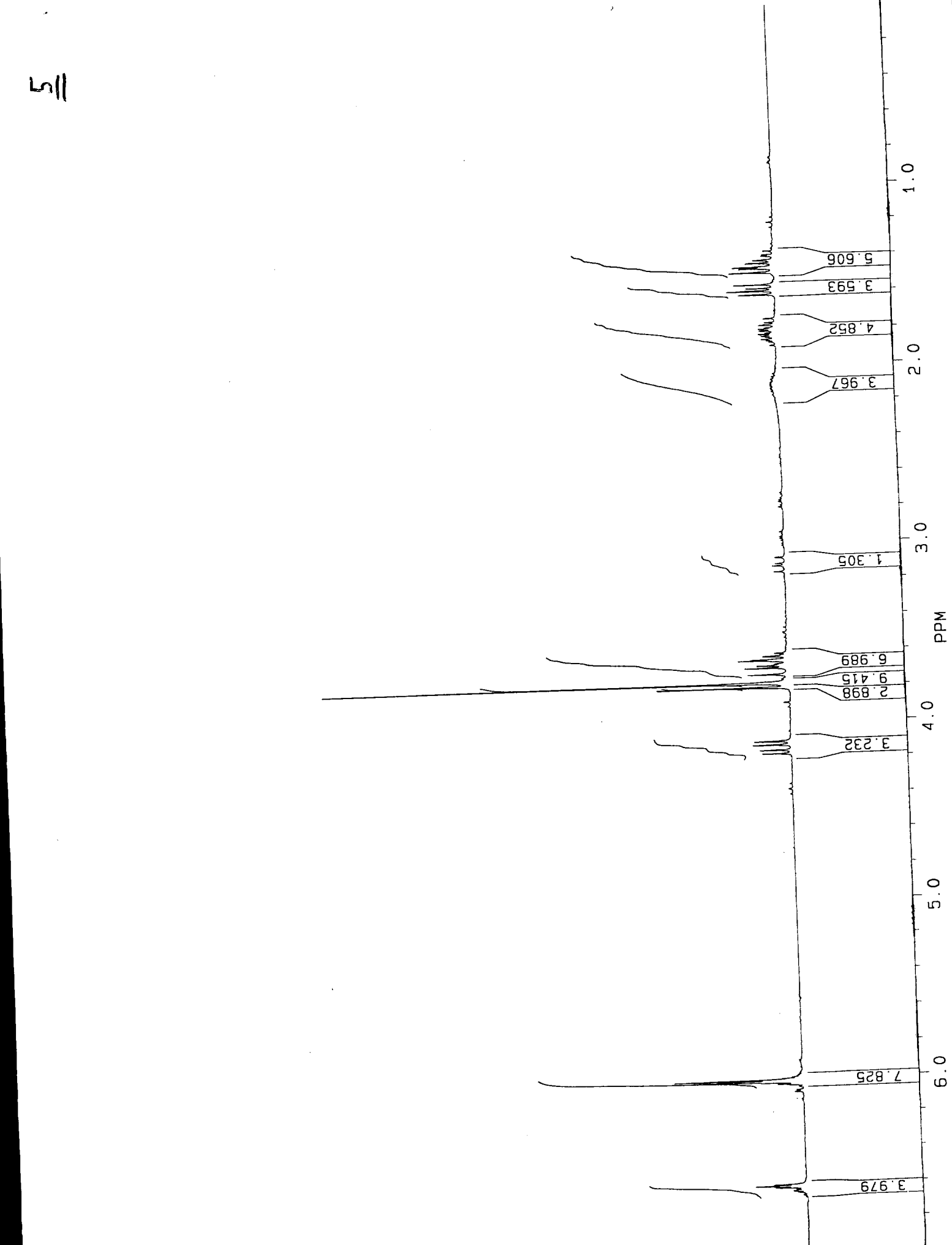

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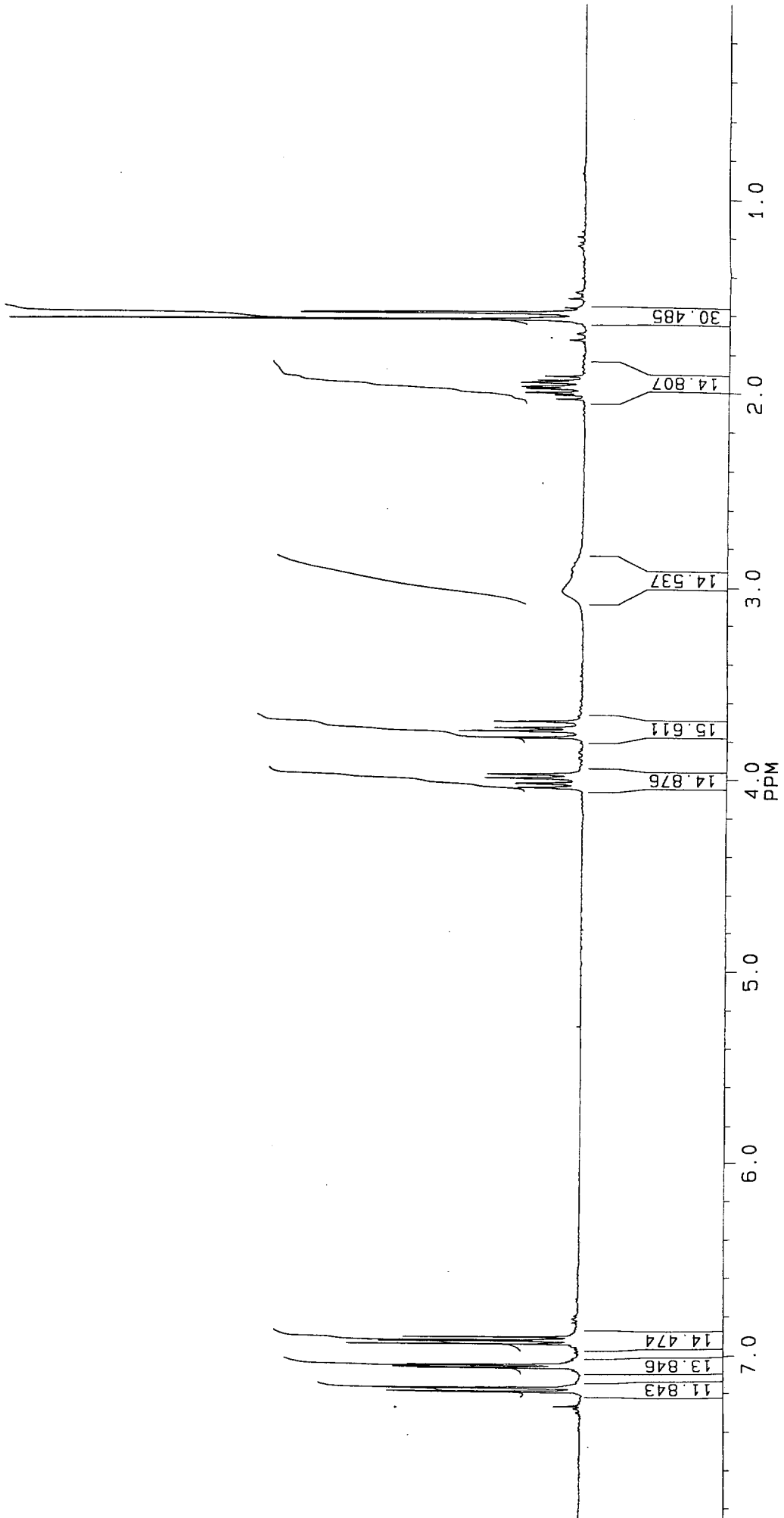

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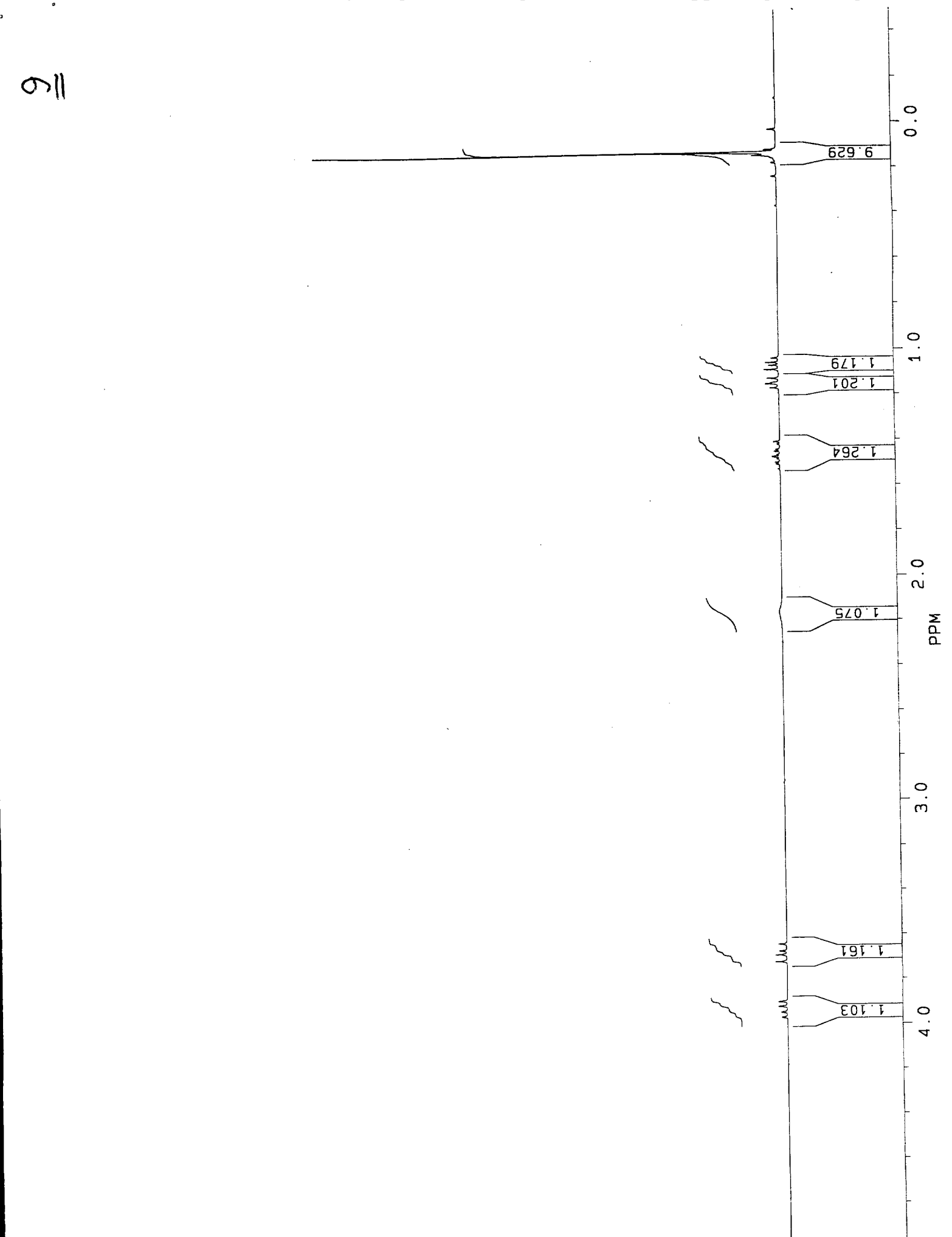

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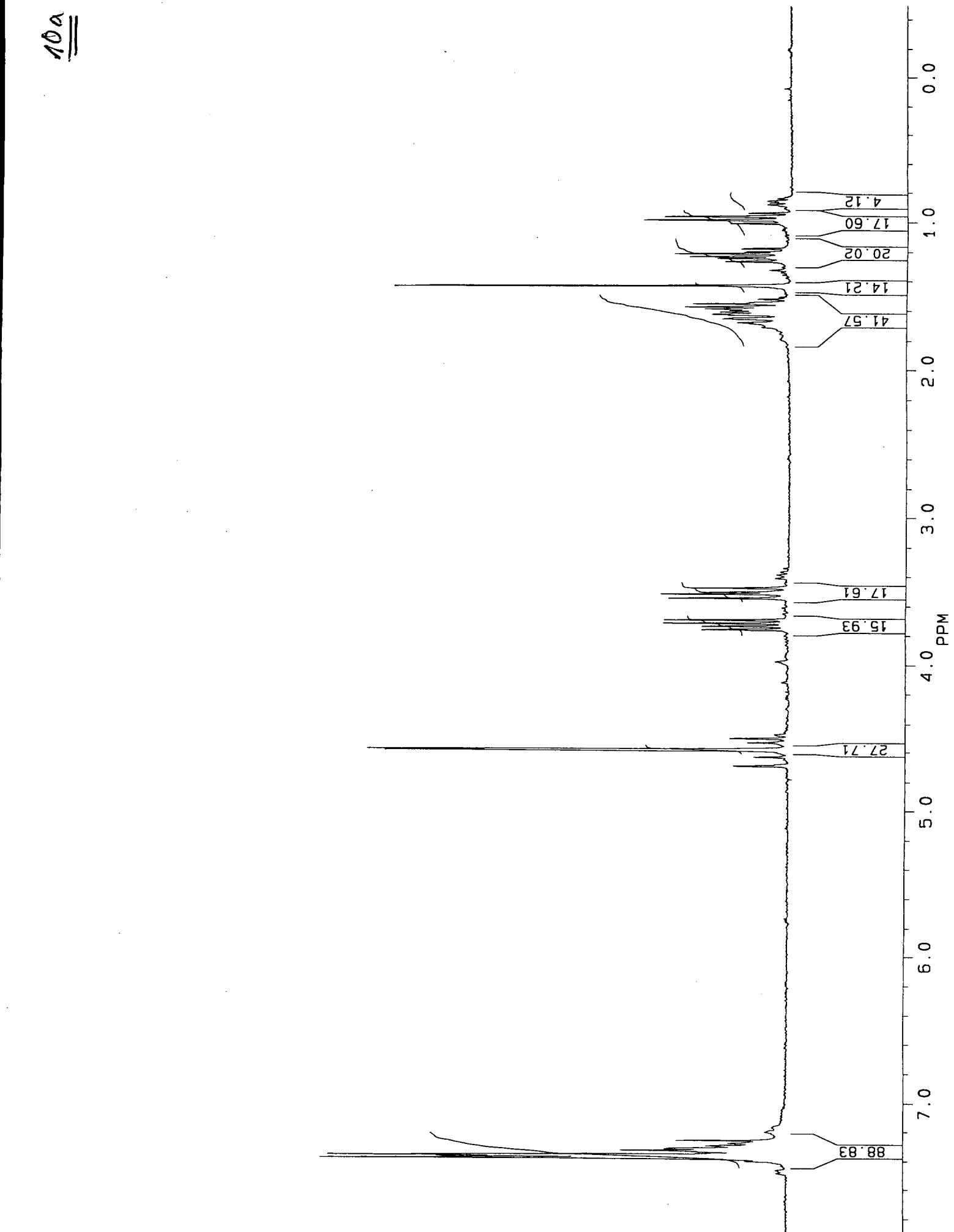

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