Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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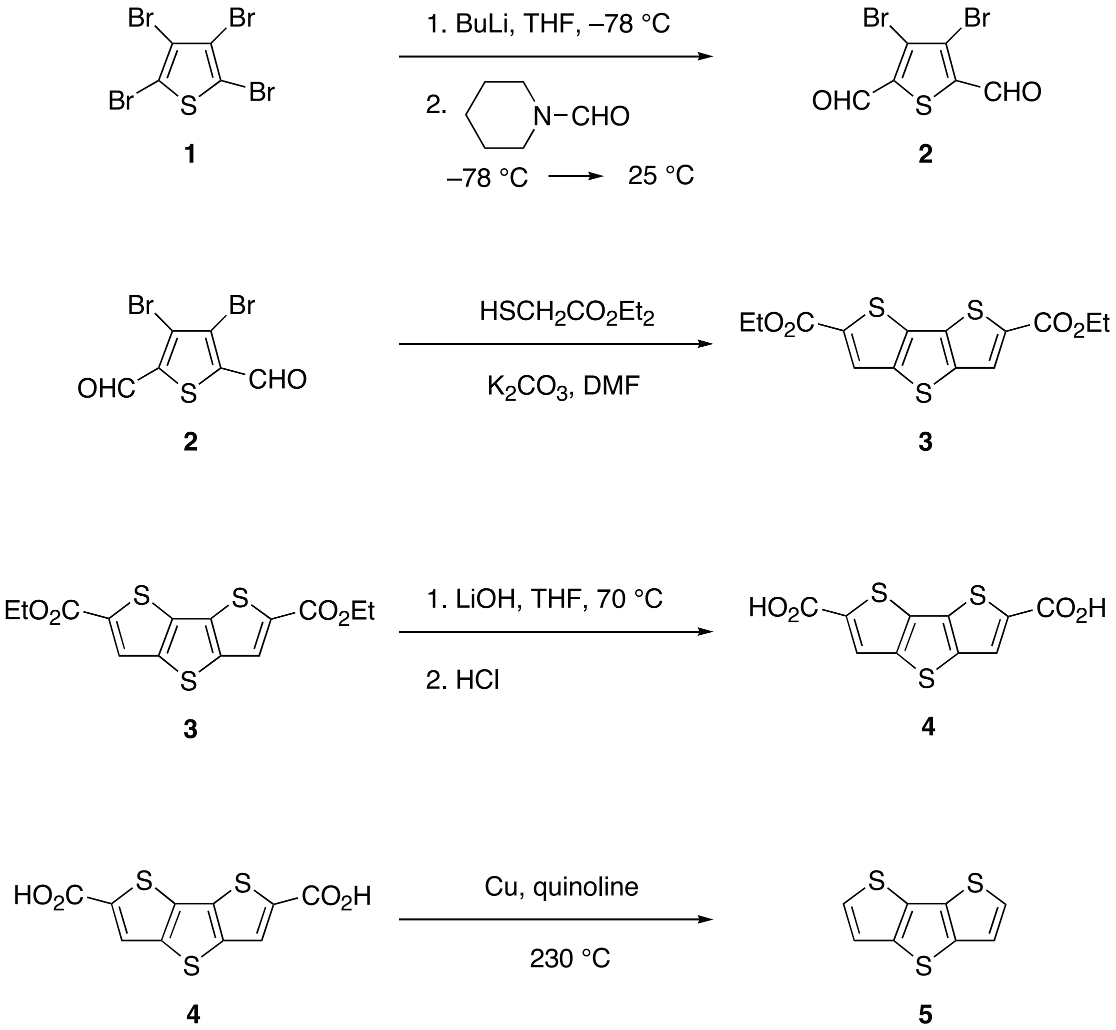
SYNTHESIS OF DITHIENO[3,2-*b*:2′,3′-*d*]THIOPHENE



Submitted by Joseph Frey, Steffen Proemmel, Michael A. Armitage, and Andrew B. Holmes.[1]

Checked by Ryo Takita and Masakatsu Shibasaki.

1. Procedure

A. 3,4-Dibromo-2,5-diformylthiophene (**2**). An oven-dried, 1-L, three-necked, round-bottomed flask is equipped with a magnetic stir bar, a low-temperature thermometer, a rubber septum and a three-way stopcock to which an argon balloon is attached. Under a gentle flow of argon, the flask is charged with tetrabromothiophene **1** (16.0 g, 40.0 mmol) (Note 1) and freshly-distilled tetrahydrofuran (200 mL) (Note 2). The solution is cooled with a dry ice/2-propanol bath to an internal temperature of less than –65 °C and a solution of butyllithium (50 mL, 1.6 M in hexanes, 80 mmol, 2 equiv) is added via syringe. The addition proceeds at a rate that keeps the internal temperature below –60 °C, usually taking 30 min. When the addition is complete, the brown solution is stirred at about –70 °C for 30 min. Dry *N*-formylpiperidine (10 mL, 90 mmol, 2.25 equiv) (Note 3) is added quickly (in about 10 s) by syringe to the reaction mixture, which is then allowed to warm slowly to ambient temperature overnight. The reaction mixture is cooled to 0 °C in an ice-water bath, and hydrochloric acid (100 mL, 6 M) is added slowly to the reaction mixture, causing a yellow precipitate to form. The mixture is stirred at 0 °C for 45 min then filtered immediately under vacuum through a sintered-glass funnel. The solid is washed with water (150 mL) and dried in the funnel under vacuum for 30 min before being dried further in a vacuum dessicator (25 mmHg, overnight, silica gel dessicant with moisture indicator) to give the crude dialdehyde **2** (8.8 g, 74%) (Notes 4, 5). The material is carried forward without further purification.

B. Dithieno[3,2-b:2',3'-d]thiophene-2,6-dicarboxylic acid diethyl ester (**3**). In an oven-dried 500-mL, two-necked, round-bottomed flask equipped with a magnetic stir bar, nitrogen inlet and rubber septum, 3,4-dibromo-2,5-diformylthiophene **2** (8.0 g, 26.9 mmol) is suspended in anhydrous *N,N*-dimethylformamide (250 mL) (Note 6). Anhydrous potassium carbonate (9.65 g, 69.8 mmol, 2.6 equiv) (Note 7) and ethyl 2-mercaptoacetate (6 mL, 55 mmol, 2.05 equiv) are added to the slurry, causing a slight exotherm, and the reaction mixture is stirred under nitrogen at ambient temperature for three days. The dark solution is poured into a beaker containing 500 mL of water stirred with a magnetic stir bar, and a yellow precipitate forms. The aqueous suspension is extracted with dichloromethane (3 x 250 mL). The red organic extracts are combined, washed with brine (4 x 500 mL) and dried over anhydrous magnesium sulfate (Note 8). After filtration through fluted filter paper, the solvents are evaporated on a rotary evaporator and a yellow solid begins to form. When the volume of solvent remaining is about 100 mL, the solid is filtered under vacuum on a Büchner funnel, washed with water (100 mL) and dried in a vacuum dessicator (7–8 mmHg, overnight, silica gel dessicant with moisture indicator) to give the crude diester **3** (6.8 g, 74%) (Note 9). The material is carried forward without further purification.

C. Dithieno[3,2-b:2',3'-d]thiophene-2,6-dicarboxylic acid (**4**). In a 500-mL, one-necked, round-bottomed flask equipped with a magnetic stir bar and reflux condenser under a static argon atmosphere (Note 10), dithieno[3,2-*b*:2',3'-*d*]thiophene-2,6-dicarboxylic acid diethyl ester **3** (5.00 g, 14.7 mmol) is suspended in tetrahydrofuran (75 mL). An aqueous solution of 1 M lithium hydroxide (75 mL, 75 mmol, 5.1 equiv.) is added (Note 11), causing the color of the suspension to change from yellow to terracotta. The mixture is heated to 70 °C (oil bath temperature) and stirring is maintained at this temperature for 4 h to give an orange solution. The solvent is evaporated on a rotary evaporator until the volume remaining is about 75 mL. A small amount of precipitate is observed. The solution is acidified with 1 M hydrochloric acid (100 mL) to give a white precipitate with some slight foam. The solid is filtered slowly under vacuum on a Büchner funnel (Note 12) and washed sequentially with water (200 mL), methanol (100 mL) and diethyl ether (100 mL). Finally, the solid is dried overnight in a high vacuum oven (40 °C, approx. 0.02 mmHg) to afford the crude diacid **4** (3.8 g, 91%) (Notes 13, 14). The material is carried forward without further purification.

D. Dithieno[3,2-b:2′,3′-d]thiophene (**5**). In a 50-mL, two-necked, round-bottomed flask equipped with a magnetic stir bar, a reflux condenser and an internal thermometer, dithieno[3,2-*b*:2′,3′-*d*]thiophene-2,6-dicarboxylic acid **4** (3.80 g, 13.4 mmol) and copper powder (0.81 g, 12.7 mmol, 0.95 equiv) (Note 15) are suspended in quinoline (25 mL). The mixture is heated to reflux at 230 °C for 1 h using a heating mantle. Petroleum ether (40–60) is added to the cooled reaction mixture and the organic layer is decanted into a 500-mL separatory funnel (Note 16). This process is repeated several times until the volume of the organic layer is about 150 mL. The organic phase is washed with 2 M hydrochloric acid (3 x 70 mL) and brine (3 x 100 mL). The organic layer is then dried over anhydrous magnesium sulfate, filtered through a fluted filter paper and the solvent is removed on a rotary evaporator to give a pale yellow oil. The residue is dissolved in a small amount of dichloromethane and filtered through a short (about 8 cm length x 5.5 cm diameter) column of silica (Note 17), using petroleum ether (40-60) as eluent. The eluent is concentrated on a rotary evaporator to give a white crystalline solid. The solid is recrystallized by dissolving in 2 mL of dichloromethane at 30 °C, adding methanol dropwise at a rate of one drop every 5 seconds to the solution until it becomes cloudy (about 5 mL), adding another drop of dichloromethane to remove the cloudiness and allowing the solution to cool to ambient temperature for 30 min. The resulting crystals are collected under vacuum on a Büchner funnel, washed with ice-cold methanol (10 mL), dried in the funnel under vacuum and transferred to an appropriate vial to be further dried in a vacuum dessicator (25 mmHg, overnight, silica gel dessicant with moisture indicator) to give the purified dithieno[3,2-*b*:2′,3′-*d*]thiophene **5** (1.9 g, 72%) (Note 18).

2. Notes

1. Tetrabromothiophene (99+%) and ethyl 2-mercaptoacetate (99%) were purchased from Acros Organics and were used as received. Butyllithium (1.6 M solution in hexanes) was purchased from Aldrich.
2. Tetrahydrofuran was distilled from sodium benzophenone ketyl.
3. *N*-Formylpiperidine (98%) was purchased from Lancaster Synthesis and dried over activated 4Å molecular sieves before use. The molecular sieves were activated in a round-bottomed flask that was heated in a microwave oven (50 W) at full power for 5 min, then evacuated under vacuum (7–8 mmHg) on a vacuum line for 5 min while being allowed to cool to room temperature. This procedure was repeated three times. The flask was sealed with a three-way cock until the activated sieves were used. *N*-Formylpiperidine was dried by standing in a sealed bottle over activated MS 4Å at room temperature overnight. The submitters found that some mono-aldehyde [^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (s, 1 H), 9.94 (s, 1 H)] was formed if the *N*-formylpiperidine was insufficiently dry.
4. All analytical thin layer chromatography analyses (TLC) were carried out on Merck pre-coated 0.25 mm thick plates of silica gel 60 F_{254}. The plates were visualized with 254 nm UV light followed by a phosphomolybdic acid solution (10% w/v in MeOH) stain.
5. The submitters report yields that range from 69–80%. The crude product has the following properties; R_f = 0.30 (5:1, hexane:ethyl acetate); mp 225 °C (sub.) (lit.,[2] 227 °C); IR (solid): 1663 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.07 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 123.7, 142.3, 183.3; LRMS (ESI) *m/z* 425 [M + 2(*i*-PrOH) + Li], 723 [2M + 2(*i*-PrOH) + Li]; Anal. Calcd for $C_6H_2O_2SBr_2$: C, 24.19; H, 0.68. Found: C, 24.25; H, 0.90.
6. Anhydrous *N*,*N*-dimethylformamide (99.8%) and lithium hydroxide monohydrate were purchased from Aldrich Chemical Company and were used as received.
7. Anhydrous potassium carbonate (>99%) was purchased from Wako Pure Chemical Industries and was used as received. In the submitter’s

case, anhydrous potassium carbonate (>99%) was purchased from Fisher Scientific UK and was used as received.

8. Anhydrous magnesium sulfate (99%) was purchased from Wako Pure Chemical Industries and was used as received. In the submitter's case, anhydrous magnesium sulfate (99%) was purchased from BDH and was used as received.

9. The submitters report yields that range from 69–71%. The crude product has the following properties; $R_f = 0.40$ (5:1, hexane:ethyl acetate); mp 189–190 °C (lit.,[3] 196 °C); IR (solid): 2983, 2934, 1715, 1691, 1228 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.41 (t, $J = 7.5$ Hz, 6 H), 4.40 (q, $J = 7.5$ Hz, 4 H), 8.00 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.5, 61.8, 126.8, 135.4, 136.0, 143.4, 162.2; LRMS (ESI (+)) *m/z* 363 [M + Na], 703 [2M + Na]; Anal. Calcd for $C_{14}H_{12}O_4S_3$: C, 49.39; H, 3.55. Found: C, 49.23; H, 3.44.

10. A static inert atmosphere was provided by attaching a three-way cock with an argon balloon at the top of the condenser. The flask was flushed with argon after the addition of reagents.

11. The aqueous solution of lithium hydroxide was prepared by dissolving 3.15 g (75 mmol) of lithium hydroxide monohydrate (Aldrich) in 75 mL of distilled water.

12. Filter paper purchased from Toyo Roshi Kaisha (No.2) was used. The checkers observed some clogging or a partial leak of a small amount of solid. The submitters used Whatman filter paper No. 54 (hardened, ashless).

13. The submitters report yields that range from 95–96%. The crude product has the following properties; mp >300 °C; IR (solid) cm^{-1}: 3083-2557 br, 1692, 1661; ^1H NMR (500 MHz, DMSO-d_6) δ: 8.18 (s, 2 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 127.7, 134.3, 137.0, 143.8, 163.3. LRMS (ESI (-)) *m/z* 283 [M-H], 567 [2M-H]; Anal. Calcd for $C_{10}H_4O_4S_3$: C, 42.24; H, 1.42. Found: C, 42.32; H, 1.61.

14. Because the product is only soluble in DMSO, TLC analysis gives $R_f = 0$ in MeOH. TLC may therefore be used to verify the loss of starting material but will not confirm the formation of the product.

15. Copper powder (99+%, irregular 300 mesh) and quinoline (98+%) were purchased from Lancaster Synthesis and were used as received.

16. The organic phases are decanted to separate the product from the insoluble copper salts.

17. Column chromatography was performed using silica gel (Merck silica gel 60 (230–400 mesh)).

18. The submitters report yields that range from 59–71%. The purified product has the following properties; $R_f = 0.33$ (hexane); mp 66–67 °C (lit.,[4] 66–67 °C); IR (solid) cm^{-1}: 3096, 3074, 1464, 1357; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.29 (d, $J = 5.5$ Hz, 2 H), 7.36 (d, $J = 5.5$ Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 120.9, 125.9, 131.0, 141.7; LRMS (ESI (+)) *m/z* 305 [M+Ag], 501 [2M+Ag]; Anal. Calcd for $C_8H_4S_3$: C, 48.95; H, 2.05. Found: C, 48.69; H, 2.20.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

In recent years much interest has been directed to dithieno[3,2-*b*:2′,3′-*d*]thiophene (DTT) **5** as a unit in semiconducting organic materials.[5-8] In particular, the dimer α,α′-bis(dithieno[3,2-*b*:2′,3′-*d*]thiophene)[9] and its derivatives[10] have been used as high mobility semiconductors in field-effect transistors, with field-effect mobilities of up to 0.05 $cm^2V^{-1}s^{-1}$ being recorded.[9]

The most recent syntheses of DTT were reported in 2002, by Hellberg and coworkers[11] in Sweden, and by Holmes and Frey[3] in Cambridge, UK. Both of these routes showed improvements over the previous method, which was published by De Jong in 1971.[4] Although the route reported by Hellberg appears to be more convenient in having fewer synthetic steps, the present method has several advantages. Each of the intermediates is a solid that requires no purification before taking forward, thus providing a quick and efficient synthetic route. The final product, DTT **5**, is quickly purified by flash column chromatography followed by recrystallization. Finally, the synthesis may be carried out on scales of over 30 g, although the lithiation step is limited on a laboratory scale due to the difficulty in cooling large-scale glassware.

DTT can be brominated in the 2- and 6- positions with NBS. This dibromide can be used in a variety of cross coupling reactions to form interesting conjugated oligomers and polymers. In addition, a novel silylation procedure can introduce TMS groups to the 3- and 5- positions.[3]

1. Melville Laboratory for Polymer Synthesis, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, U.K. and School of Chemistry, University of Melbourne, Vic. 3010, Australia.; Bio21 Institute, University of Melbourne, Vic. 3010, Australia.
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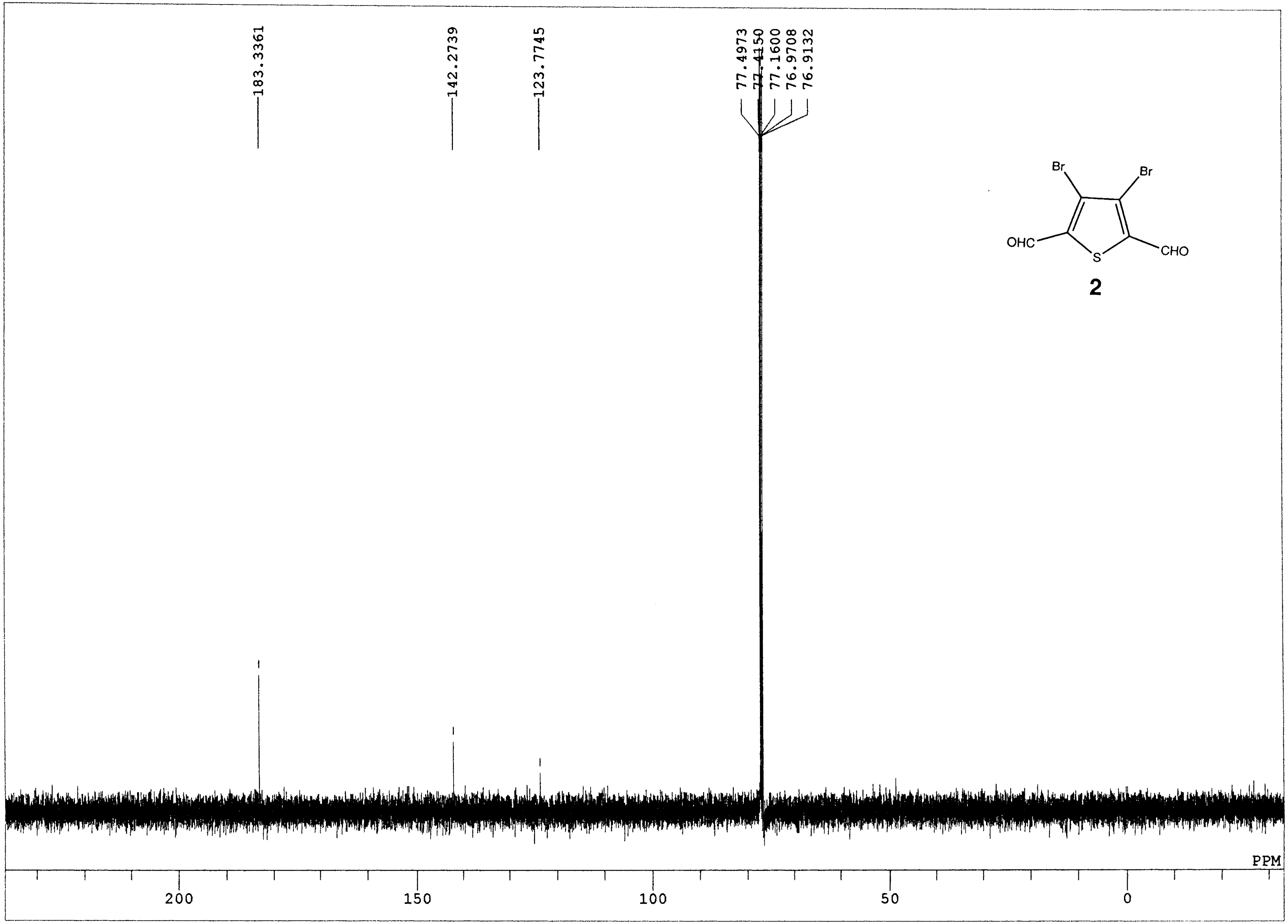
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Tetrabromothiophene; (3958-03-0)
N-Formylpiperidine: 1-Piperidinecarboxaldehyde; (2591-86-8)
3,4-Dibromo-2,5-diformylthiophene: 2,5-Thiophenedicarboxaldehyde, 3,4-dibromo-; (25373-20-0)
Ethyl 2-mercaptoacetate: Acetic acid, mercapto-, ethyl ester; (623-51-8)
Dithieno[3,2-b:2',3'-d]thiophene-2,6-dicarboxylic acid diethyl ester; 216 (502764-52-5)
Dithieno[3,2-b:2',3'-d]thiophene-2,6-dicarboxylic acid; (502764-53-6)
Dithieno[3,2-b:2',3'-d]thiophene; (593-75-7)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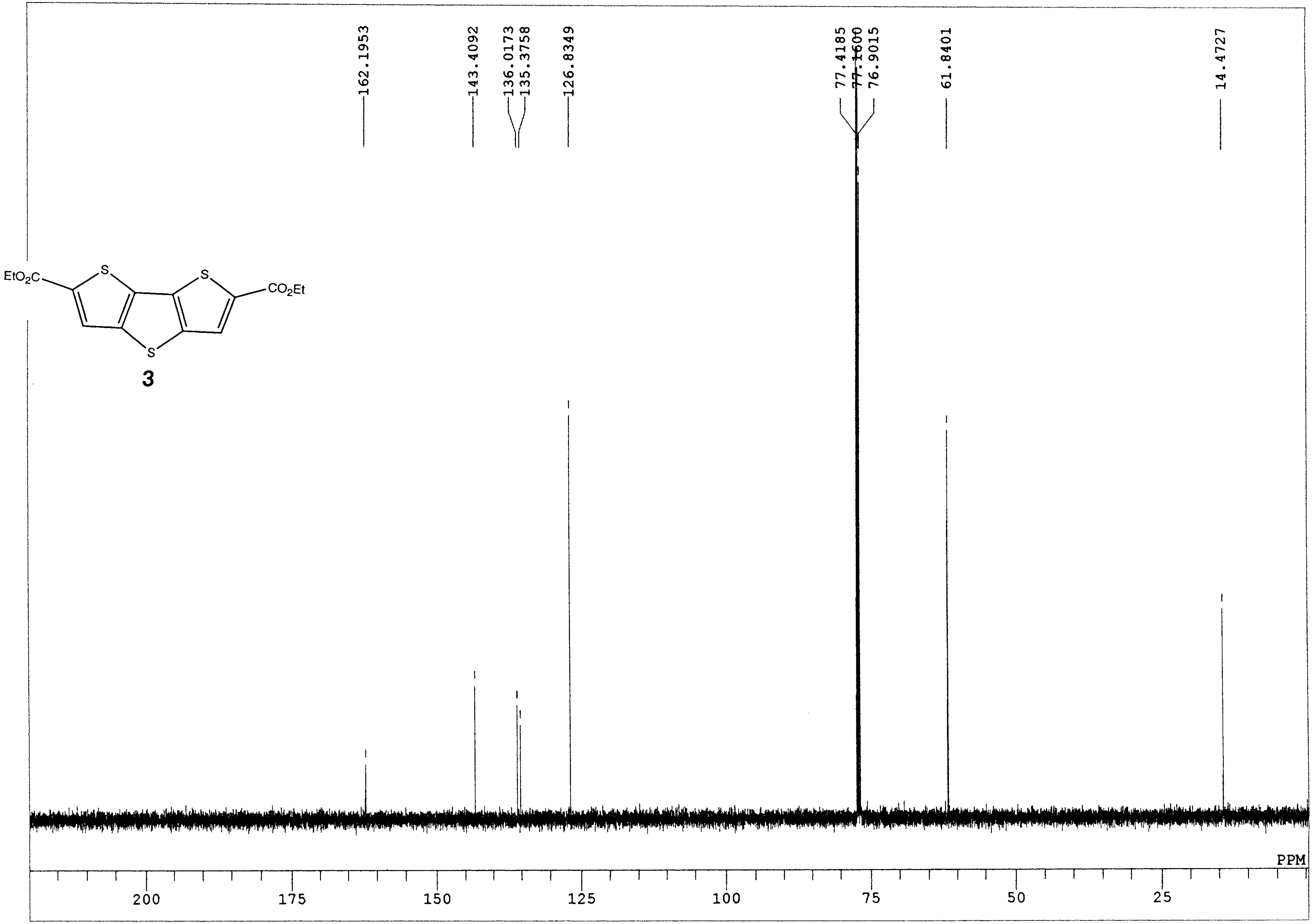
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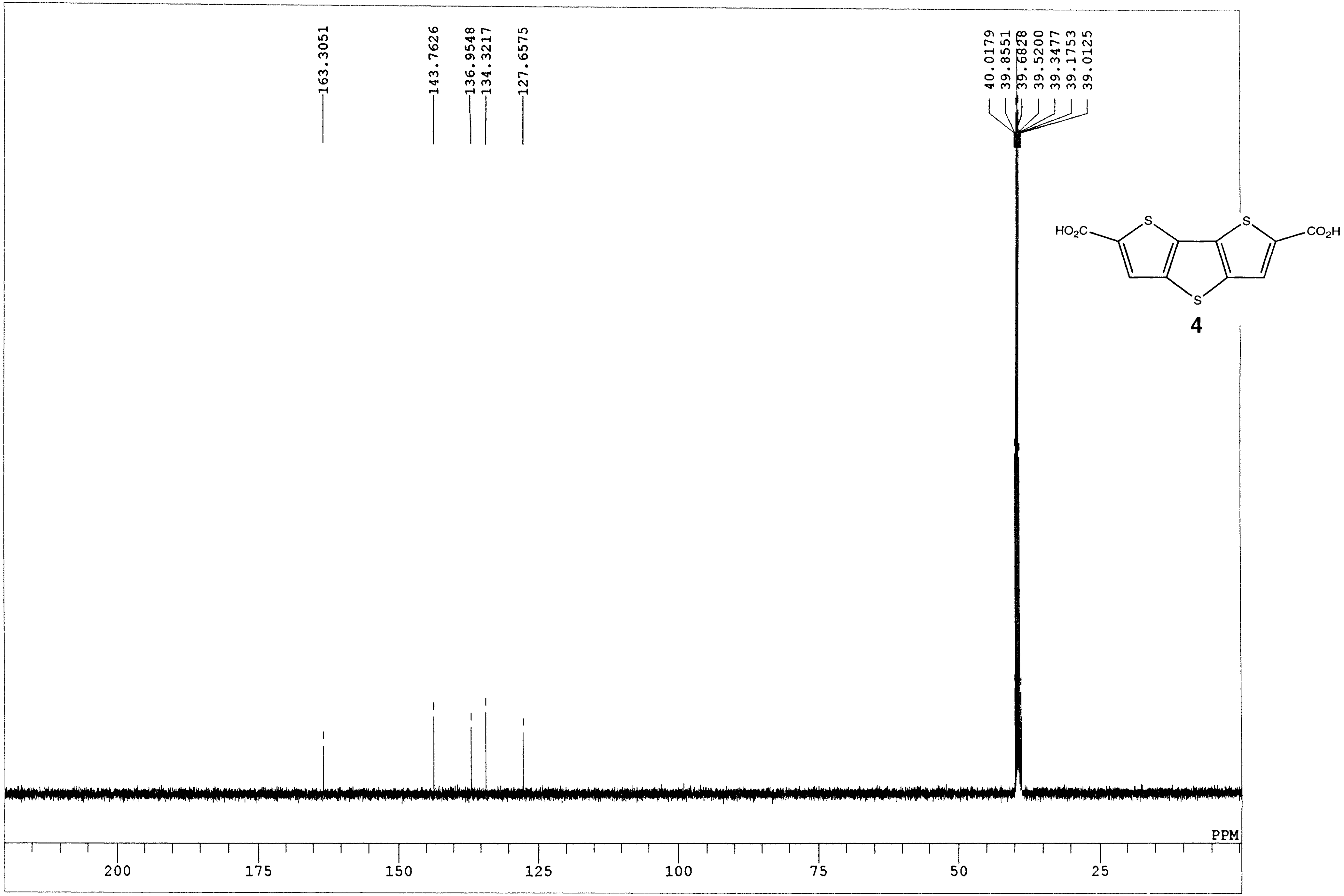
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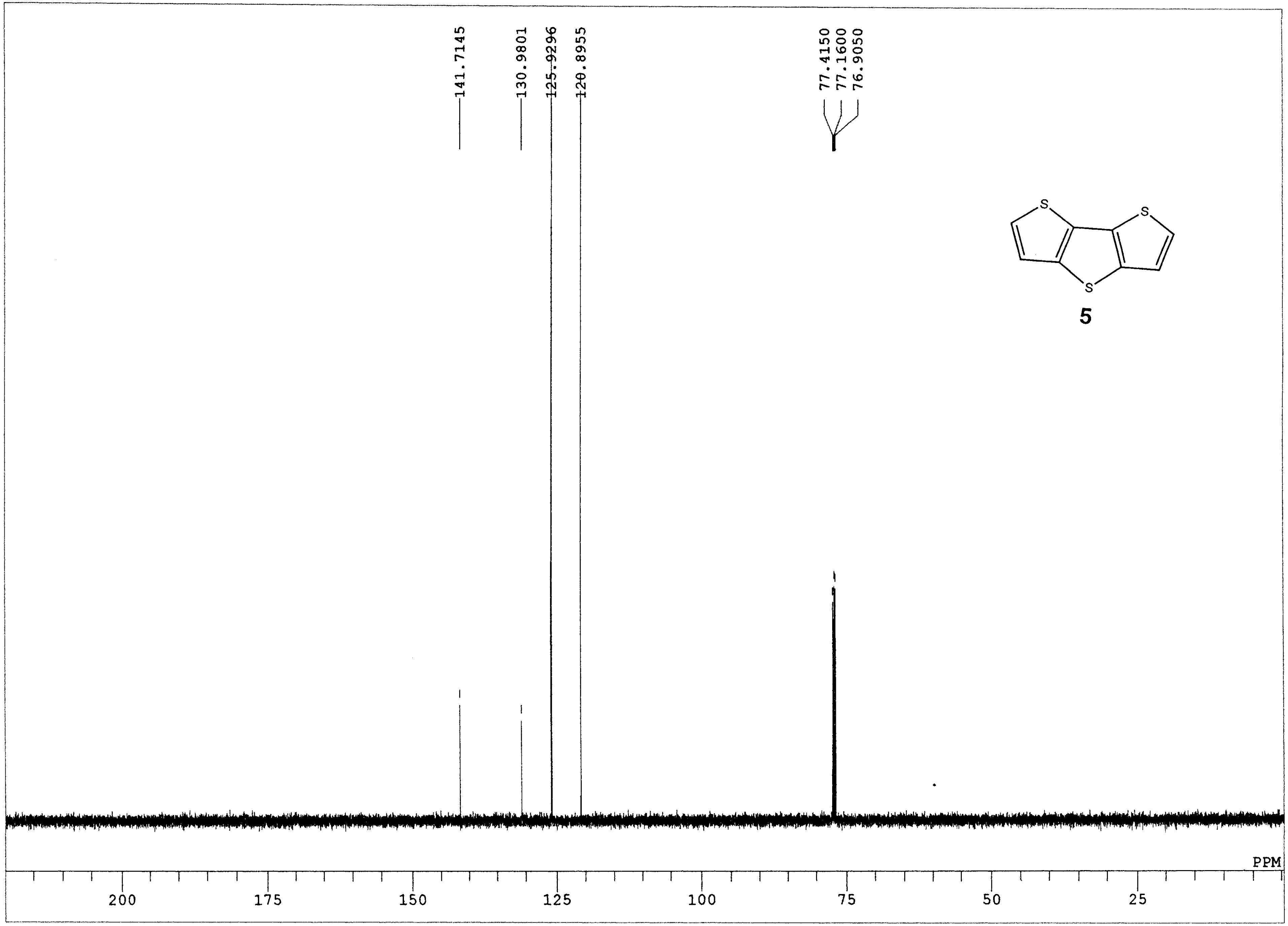
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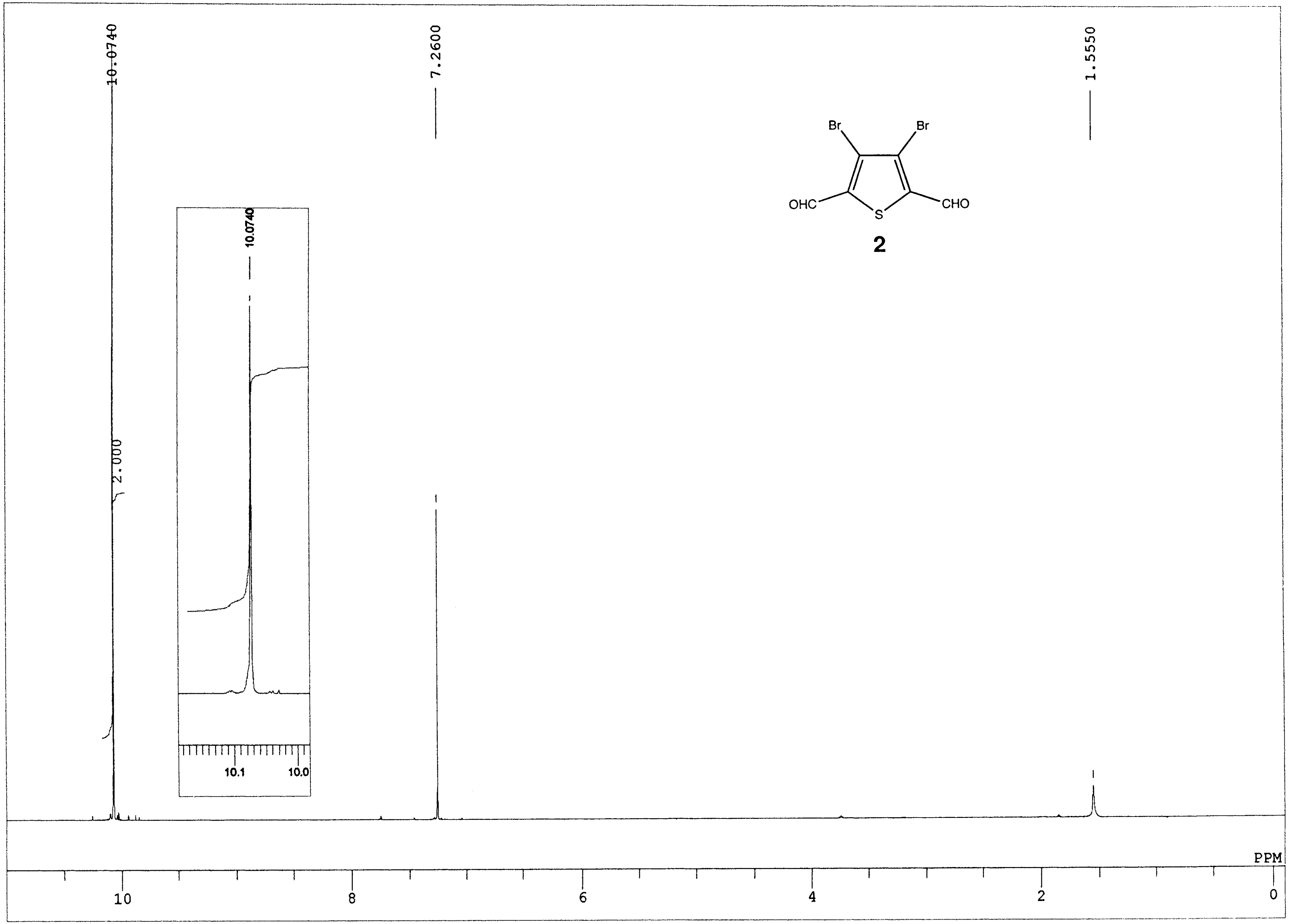

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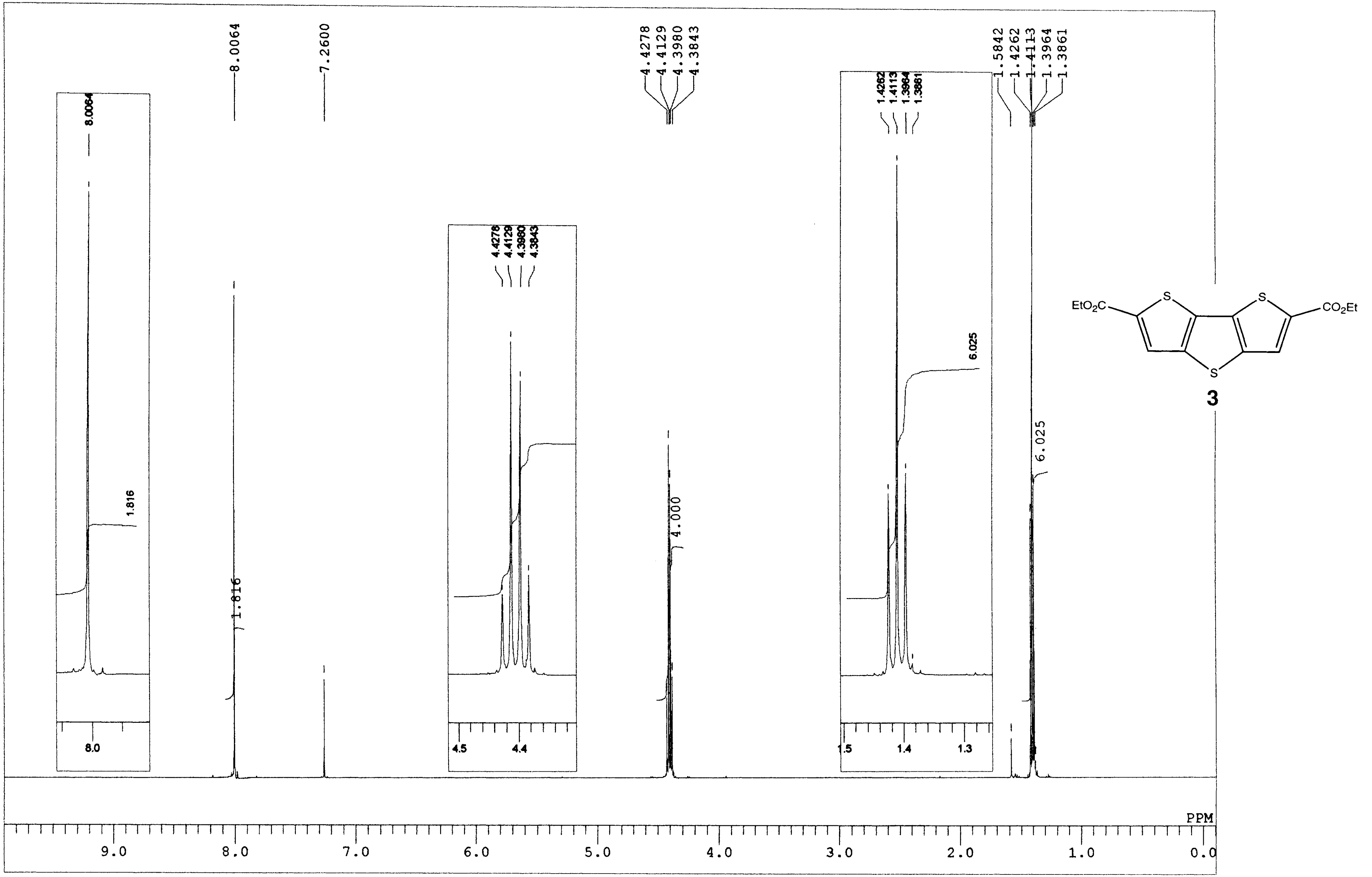
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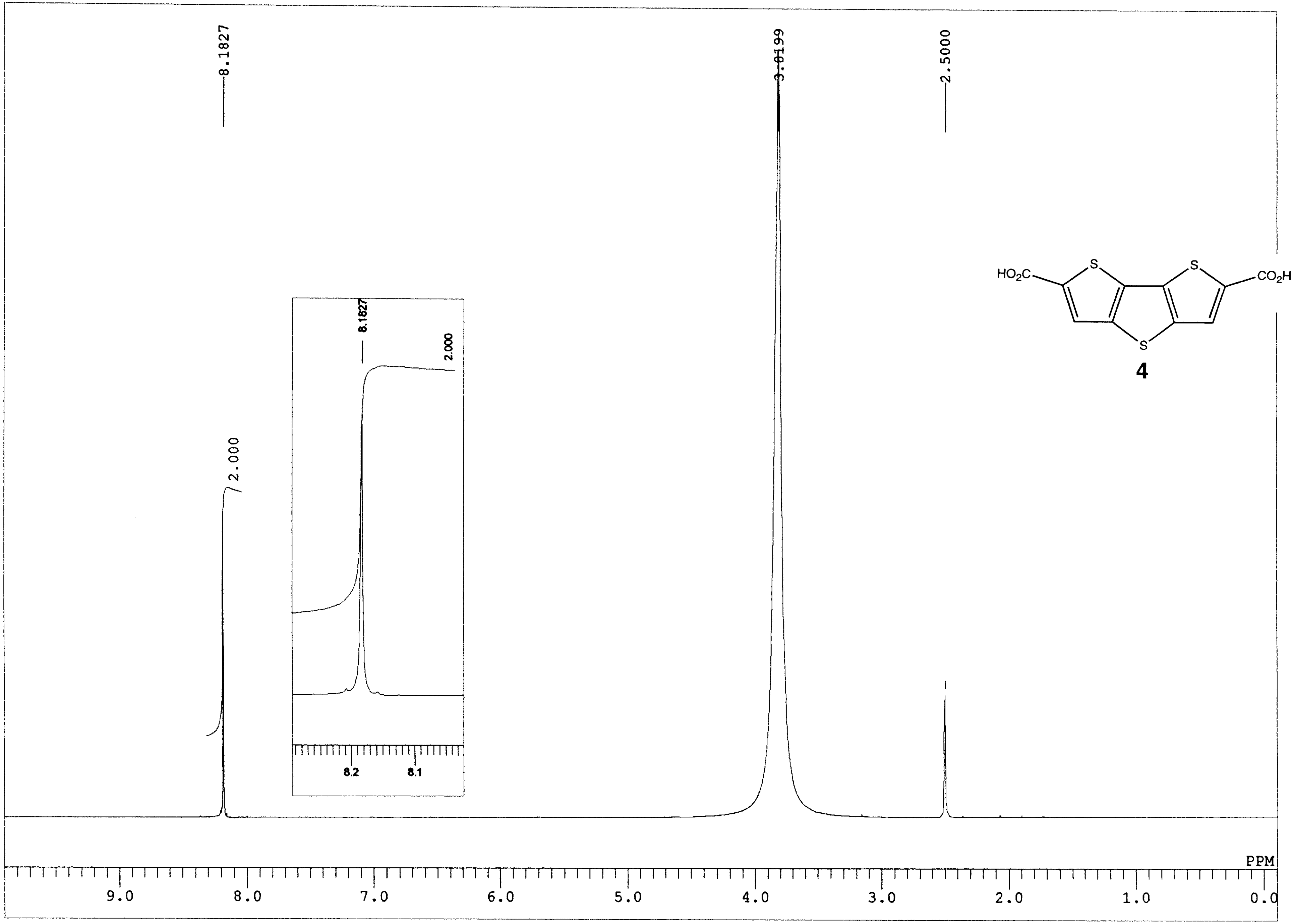
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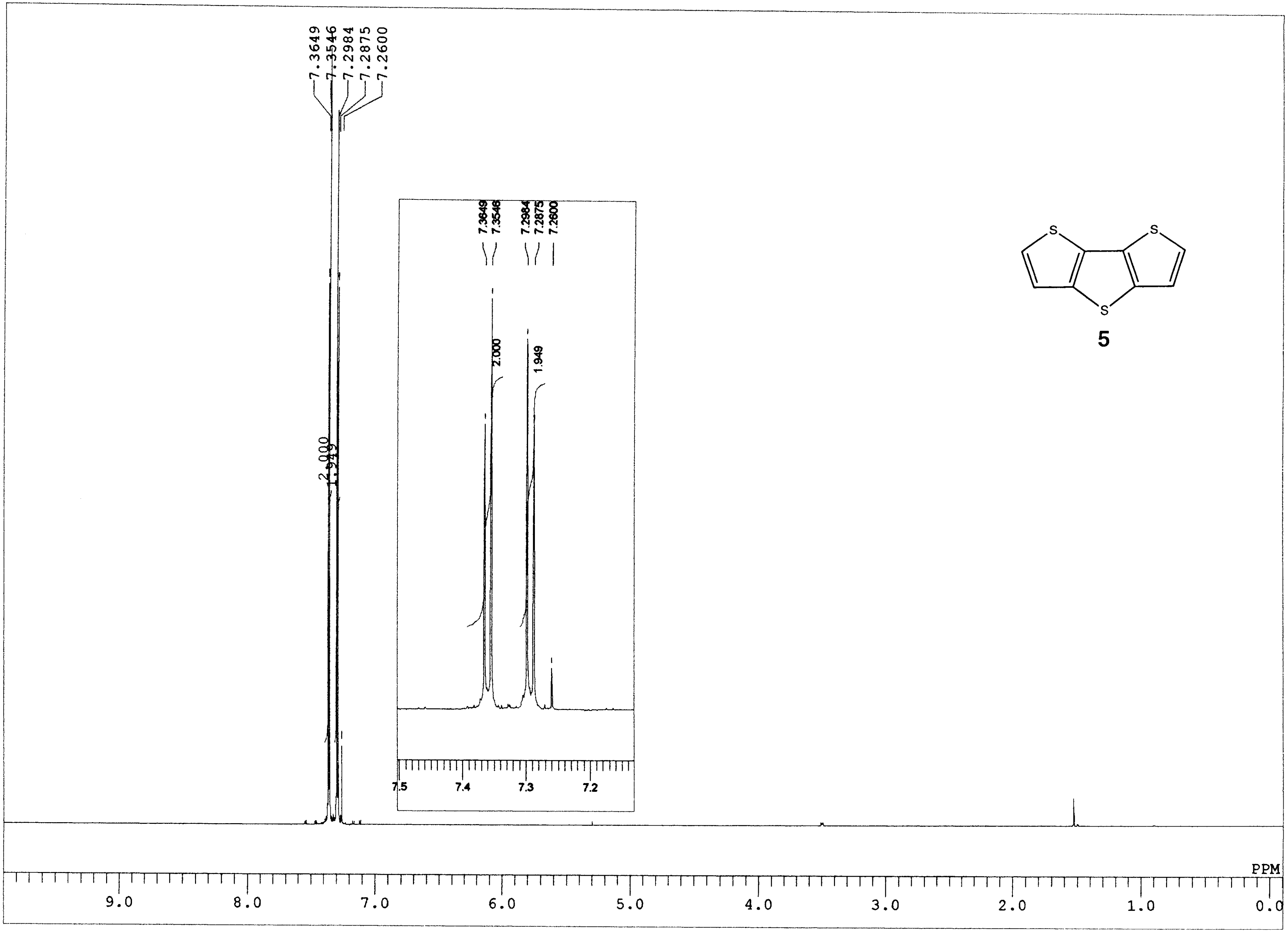
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