

**Synthesis of Isoquinolines and Pyridines by the Palladium- and
Copper-Catalyzed Coupling and Cyclization of Terminal Acetylenes**

Kevin R. Roesch and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames IA 50011

Supporting Information

General Procedure for the Copper-Catalyzed Cyclization of Iminoalkynes. DMF (5 mL), the imine (0.25 mmol), and CuI (5 mg, 0.025 mmol), were placed in a 2 dram vial. The vial was flushed with nitrogen and heated in an oil bath at 100 °C for the indicated period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with 25 mL of ether, washed with 30 mL of saturated NH₄Cl, dried (Na₂SO₄), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

Compounds Prepared

3-Phenylisoquinoline (2). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 51 mg (100%) of the indicated compound with

spectral properties identical to those previously reported¹: mp 102-103 °C (lit.¹ mp 101-102 °C).

3-(Cyclohex-1-enyl)isoquinoline (3). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 42 mg (81%) of the indicated compound as a yellow solid: mp 114-115 °C (hexanes/EtOAc); ¹H NMR (CDCl₃) δ 1.67-1.75 (m, 2H), 1.81-1.89 (m, 2H), 2.29-2.36 (m, 2H), 2.54-2.60 (m, 2H), 7.02 (tt, *J* = 2.4, 3.6 Hz, 1H), 7.48 (dt, *J* = 0.6, 14.4 Hz, 1H), 7.57 (s, 1H), 7.63 (dd, *J* = 1.2, 6.9 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 9.18 (s, 1H); ¹³C NMR (CDCl₃) δ 22.3, 23.1, 26.1, 26.2, 114.2, 126.4, 126.8, 127.6, 128.4, 130.3, 135.7, 136.7, 151.7, 152.5 (one sp² carbon missing due to overlap); IR (CHCl₃, cm⁻¹) 3060, 2919, 1621, 1574; MS *m/z* (rel intensity) 209 (100, M⁺), 208 (89), 194 (42), 180 (51). Anal. Calcd for C₁₅H₁₅N: C, 86.09; H, 7.23; N, 6.69. Found: C, 86.03; H, 7.30; N, 6.73.

3-Cyclohexylisoquinoline (4). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 49 mg (93%) of the indicated compound as a yellow oil, which solidified upon cooling: mp 40-41 °C (hexanes/EtOAc); ¹H NMR (CDCl₃) δ 1.25-1.67 (m, 6H), 1.89 (dt, *J* = 2.7, 12.6 Hz, 2H), 2.06 (dd, *J* = 1.5, 12.9 Hz, 2H), 2.84 (tt, *J* = 3.3, 11.7 Hz, 1H), 7.45 (s, 1H), 7.50 (ddd, *J* = 1.2, 6.9, 8.1 Hz, 1H), 7.62 (td, *J* = 1.2, 6.9 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 9.19 (s, 1H); ¹³C NMR (CDCl₃) δ 26.3, 26.8, 33.2, 46.2, 116.2, 126.3, 126.4, 127.3, 127.5, 130.2, 136.7, 151.9, 160.2; IR (CHCl₃, cm⁻¹) 3055, 2926, 1628, 1585; HRMS Calcd for C₁₅H₁₇N: 211.1356. Found: 211.1361.

**General Procedure for the Palladium and Copper-Catalyzed
Formation of Isoquinolines and Pyridines from Terminal Acetylenes.**

Et₃N (2 mL), PdCl₂(PPh₃)₂ (7 mg, 0.01 mmol), the imine (0.5 mmol), the terminal acetylene (0.6 mmol) and CuI (1 mg, 0.005 mmol) were placed in a 2 dram vial. The vial was flushed with nitrogen and heated in an oil bath at 55 °C for the indicated period of time. The reaction was monitored by TLC to establish completion. For the reactions with imine **1**, the reaction mixture was cooled, the precipitates were filtered off and washed with ether, and the solvent was removed under reduced pressure. For the reactions of all other imines, the reaction mixture was cooled, the solvent was removed under reduced pressure, the precipitates were filtered off and washed with ether, and the solvent was removed under reduced pressure. The residue obtained was transferred to a 2 dram vial and DMF (5 mL) and CuI (10 mg, 0.05 mmol) were added. The vial was flushed with nitrogen and heated in an oil bath at 100 °C for the indicated period of time. The reaction mixture was cooled, diluted with 25 mL of ether, washed with 30 mL of saturated NH₄Cl, dried (Na₂SO₄), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

Compounds Prepared

3-Phenylisoquinoline (2). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 94 mg (91%) of the indicated compound, whose spectral data were identical with that reported above.

3-(Cyclohex-1-enyl)isoquinoline (3). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 85 mg (81%) of the indicated compound, whose spectral data were identical with that reported above.

3-Cyclohexylisoquinoline (4). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 93 mg (88%) of the indicated compound, whose spectral data were identical with that reported above.

3-(Diethoxymethyl)isoquinoline (5). The reaction mixture was chromatographed using 4:1 hexanes/EtOAc to afford 97 mg (84%) of the indicated compound as a yellow oil: $^1\text{H NMR}$ (CDCl_3) δ 1.25 (dt, $J = 0.6, 13.5$ Hz, 6H), 3.67 (dddd, $J = 0.6, 7.2, 7.8, 16.5$ Hz, 4H), 5.67 (s, 1H), 7.54 (dddd, $J = 1.2, 1.2, 8.1, 8.1$ Hz, 1H), 7.64 (dddd, $J = 1.2, 1.2, 6.9, 6.9$ Hz, 1H), 7.82 (d, $J = 8.1$ Hz, 1H), 7.90-7.93 (m, 2H), 9.23 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3) δ 15.3, 62.0, 102.4, 117.7, 127.2, 127.5, 127.5, 128.4, 130.5, 136.2, 151.5, 152.2; IR (neat, cm^{-1}) 3056, 2975, 1629, 1587; HRMS Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2$: 231.1259. Found: 232.1338 (M+H).

7-Cyclohexyl-1,3-dioxolo[4,5-g]isoquinoline (6). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 97 mg (76%) of the indicated compound as a yellow solid: mp 93-94 °C (hexanes/EtOAc); $^1\text{H NMR}$

(CDCl₃) δ 1.20-1.61 (m, 5H), 1.71-1.77 (m, 1H), 1.85 (dt, $J = 3.0, 12.3$ Hz, 2H), 1.97-2.02 (m, 2H), 2.74 (tt, $J = 3.3, 8.1$ Hz, 1H), 6.01 (s, 2H), 6.95 (s, 1H), 7.09 (s, 1H), 7.25 (s, 1H), 8.89 (s, 1H); ¹³C NMR (CDCl₃) δ 26.3, 26.8, 33.3, 46.0, 101.4, 102.3, 103.0, 116.1, 124.3, 135.1, 147.7, 149.7, 150.8, 159.3; IR (CHCl₃, cm⁻¹) 3029, 2923, 1601, 1584, 1482, 1453; HRMS Calcd for C₁₆H₁₇NO₂: 255.1259. Found: 255.1254.

7-*n*-Butyl-1,6-naphthyridine (8). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 67 mg (72%) of the indicated compound as a yellow oil: ¹H NMR (CDCl₃) δ 0.91 (t, $J = 7.5$ Hz, 3H), 1.38 (sextet, $J = 7.5$ Hz, 2H), 1.77 (quintet, $J = 7.5$ Hz, 2H), 2.95 (t, $J = 7.5$ Hz, 2H), 7.39 (dd, $J = 4.2, 8.4$ Hz, 1H), 7.69 (s, 1H), 8.19 (dd, $J = 0.9, 8.4$ Hz, 1H), 8.99 (d, $J = 2.7$ Hz, 1H), 9.16 (s, 1H); ¹³C NMR (CDCl₃) δ 14.0, 22.5, 31.9, 38.0, 119.6, 121.7, 121.9, 135.6, 151.1, 152.4, 154.8, 160.4; IR (neat, cm⁻¹) 3051, 2942, 1604, 1481, 1456; HRMS Calcd for C₁₂H₁₄N₂: 186.1157. Found: 186.1159.

6,7-Dihydro-5*H*[2]-3-(cyclohex-1-enyl)pyridine (10). The reaction mixture was chromatographed using 7:1 hexanes/EtOAc to afford 55 mg (55%) of the indicated compound as a yellow oil: ¹H NMR (CDCl₃) δ 1.62-1.69 (m, 2H), 1.74-1.81 (m, 2H), 2.07 (quintet, $J = 7.5$ Hz, 2H), 2.22-2.25 (m, 2H), 2.47-2.49 (m, 2H), 2.88 (q, $J = 6.9$ Hz, 4H), 6.56-6.59 (m, 1H), 7.24 (s, 1H), 8.38 (s, 1H); ¹³C NMR (CDCl₃) δ 22.3, 23.0, 25.2, 26.0, 26.4, 30.1, 32.8, 115.2, 127.5, 136.9, 137.9, 144.5, 154.1, 157.2; IR (CHCl₃, cm⁻¹) 3059, 2854, 1602, 1554, 1477; HRMS Calcd for C₁₄H₁₇N: 199.1361. Found: 199.1361.

2,4-Diphenylpyridine (12). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 66 mg (57%) of the indicated compound as a yellow oil with spectral properties identical to those previously reported.²

Total synthesis of Decumbenine B

Decumbenine B (15). DMF (5 mL), Pd(OAc)₂ (3 mg, 0.013 mmol), Na₂CO₃ (26 mg, 0.25 mmol), and *N*-(4-iodobenzo[1,3]dioxol-5-yl)methylene)-*tert*-butylamine (0.083 g, 0.25 mmol) were placed in a 2 dram vial. The contents were then stirred for 1 minute and (5-ethynylbenzo[1,3]dioxol-4-yl)methanol (42 mg, 0.28 mmol) was added. The vial was flushed with nitrogen and heated in an oil bath at 100° C for 48 h. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with 25 mL of ether, washed with 30 mL of saturated NH₄Cl, dried (Na₂SO₄), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column using 1:1 hexanes/EtOAc to afford 42 mg (52%) of the indicated compound with spectral properties identical to those previously reported³: mp 221-222 °C (lit.³ mp 222-224 °C).

References

1. Sard, H. J. *Heterocycl. Chem.* **1994**, *31*, 1085.

2. (a) Katritzky, A. R.; Mazurkiewicz, R.; Stevens, C. V.; Gordeev, M. F. *J. Org. Chem.* **1994**, *59*, 2740. (b) Katritzky, A. R.; Chapman, A. V.; Cook, M. J.; Millet, G. H. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2743.
3. (a) Zhang, J.; Zhu, D.; Hong, S. *Phytochemistry* **1995**, *39*, 435. (b) Xu, X.; Qin, G.; Xu, R.; Zhu, X. *Tetrahedron* **1998**, *54*, 14179.

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2.880
2.869
2.852
2.841
2.830
2.814
2.803
2.791

2.086
2.081
2.043
2.038
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1.871
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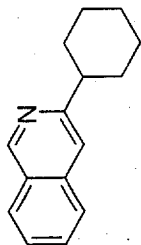
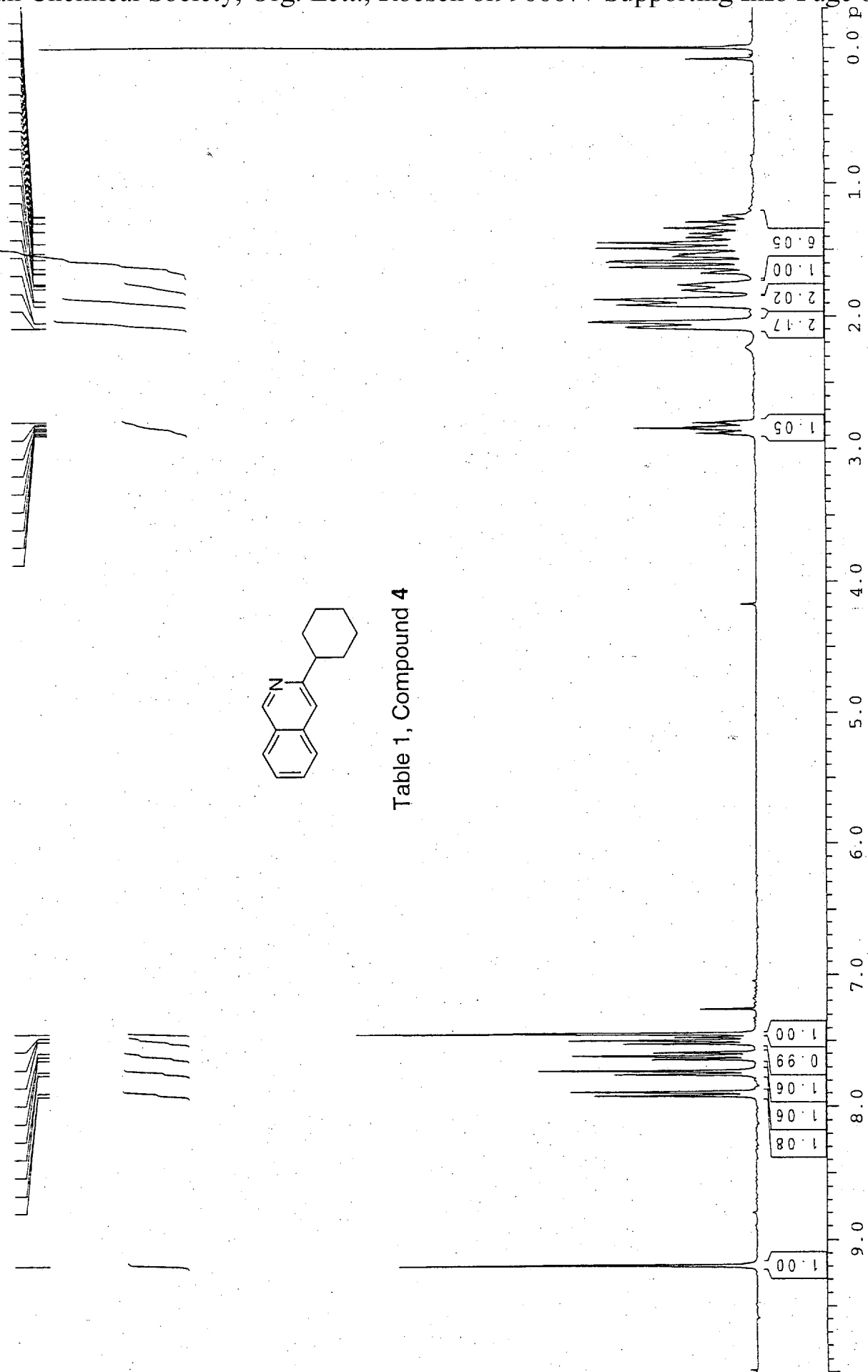


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7.445



26.277
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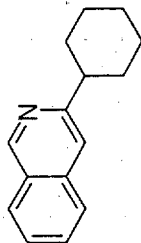


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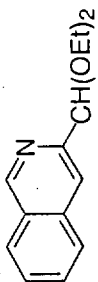
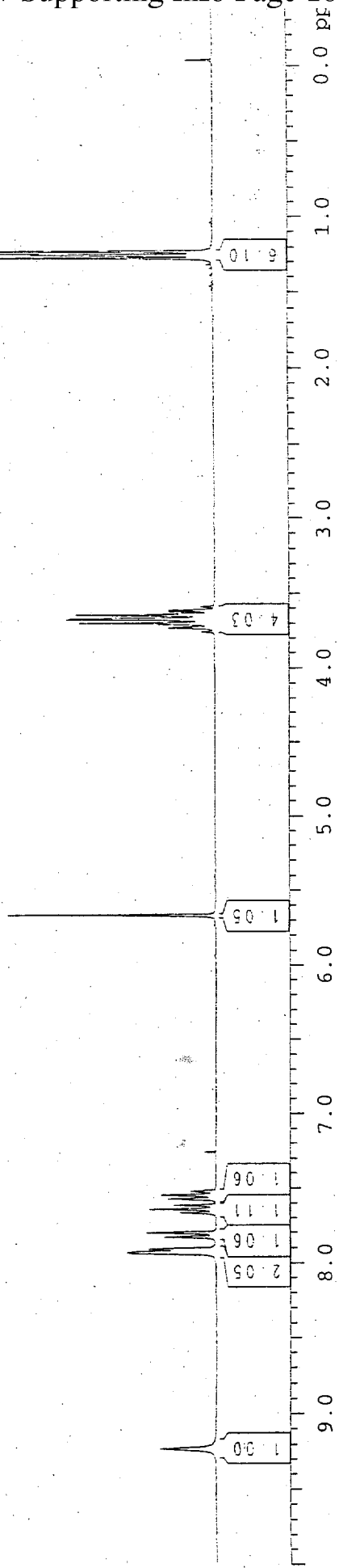


Table 1, Compound 5



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102.360

76.294

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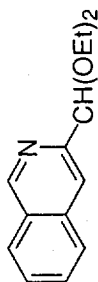
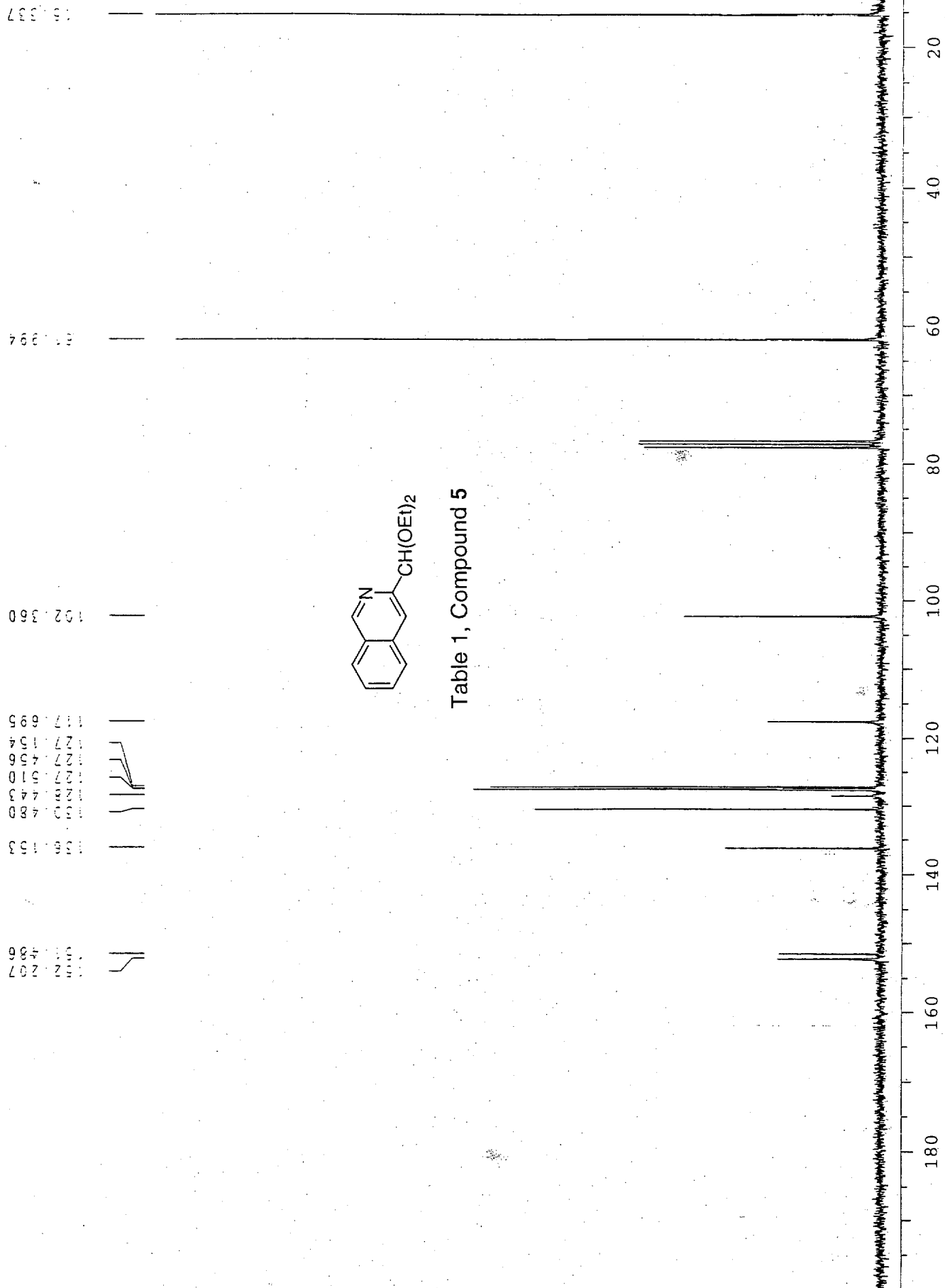


Table 1, Compound 5



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0.770
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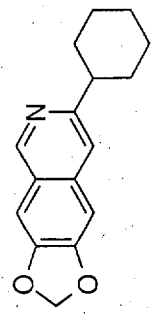
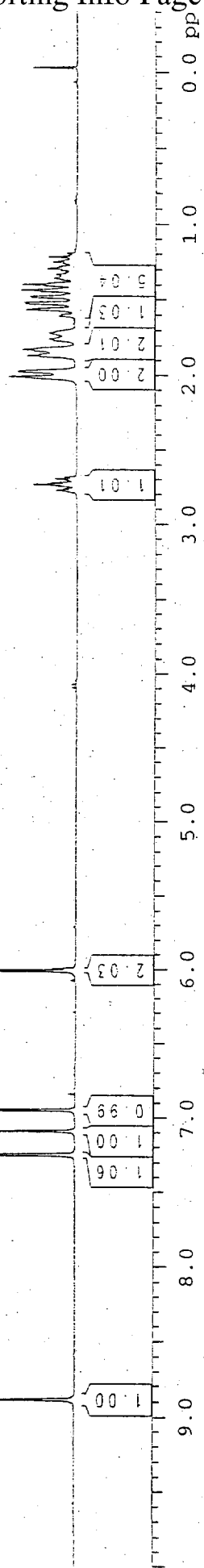


Table 1, Compound 6

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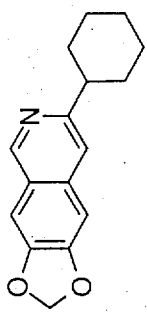


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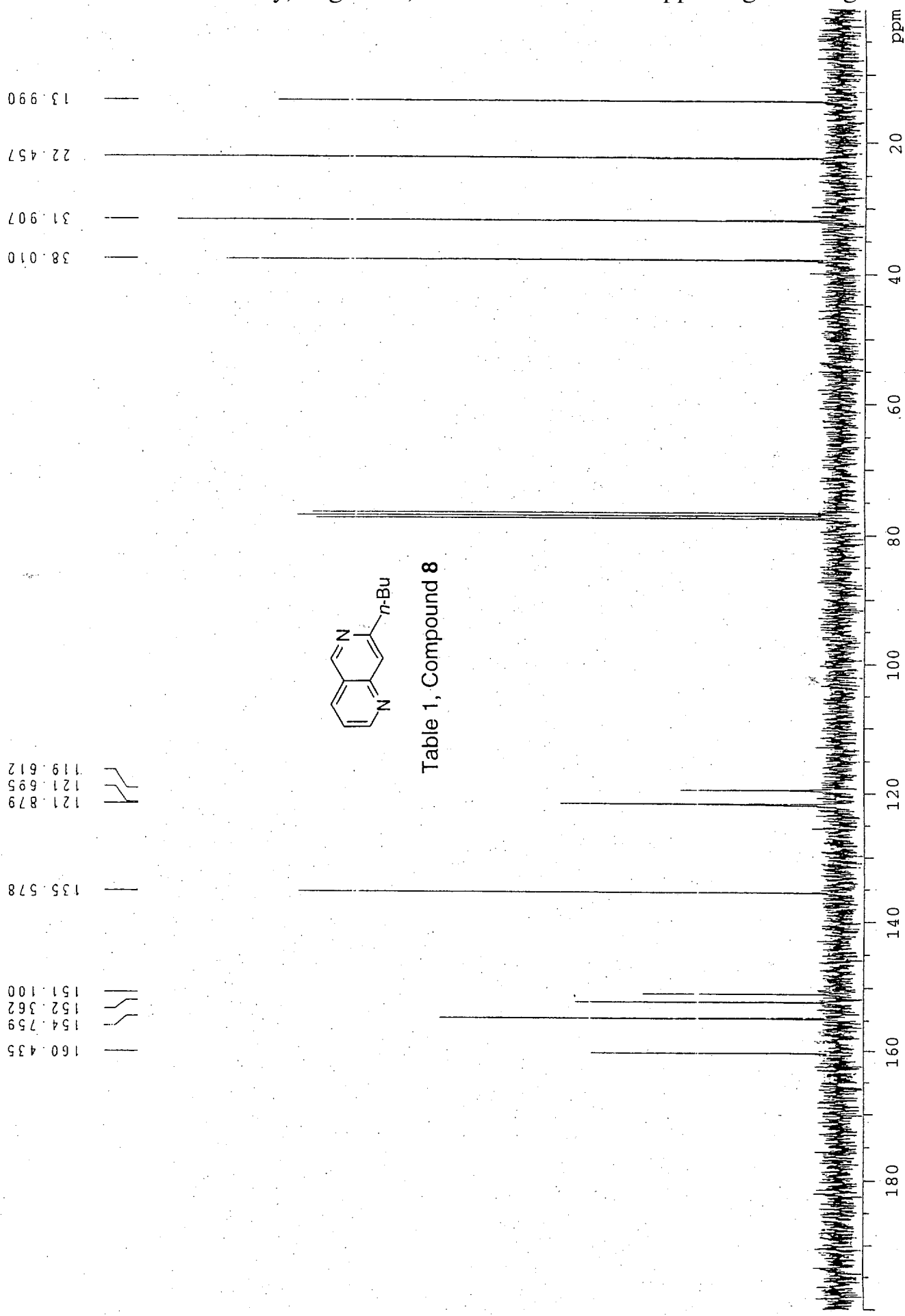


Table 1, Compound 8

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0.909
0.884

2.972
2.947
2.920

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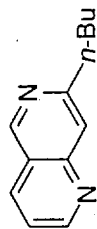
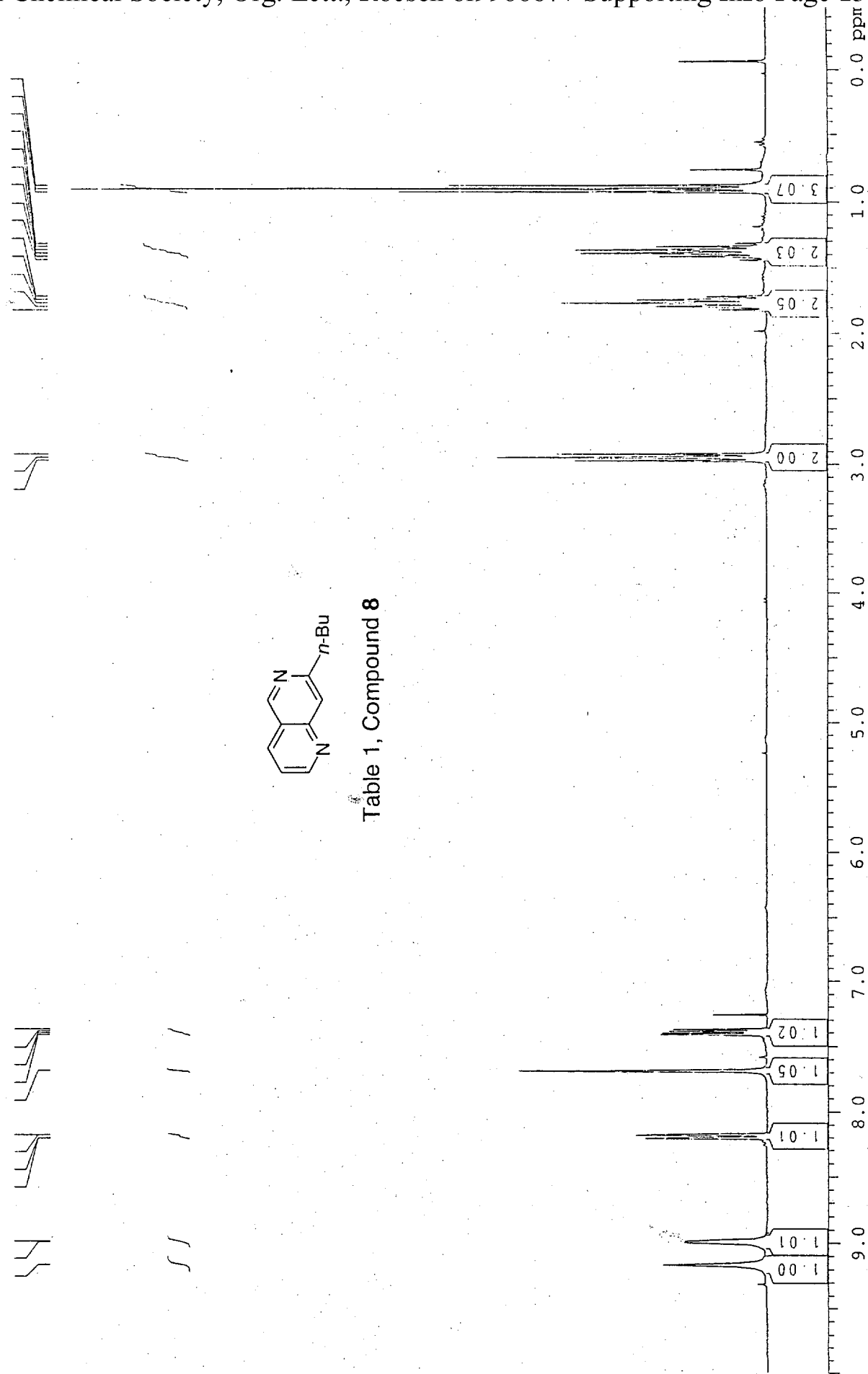
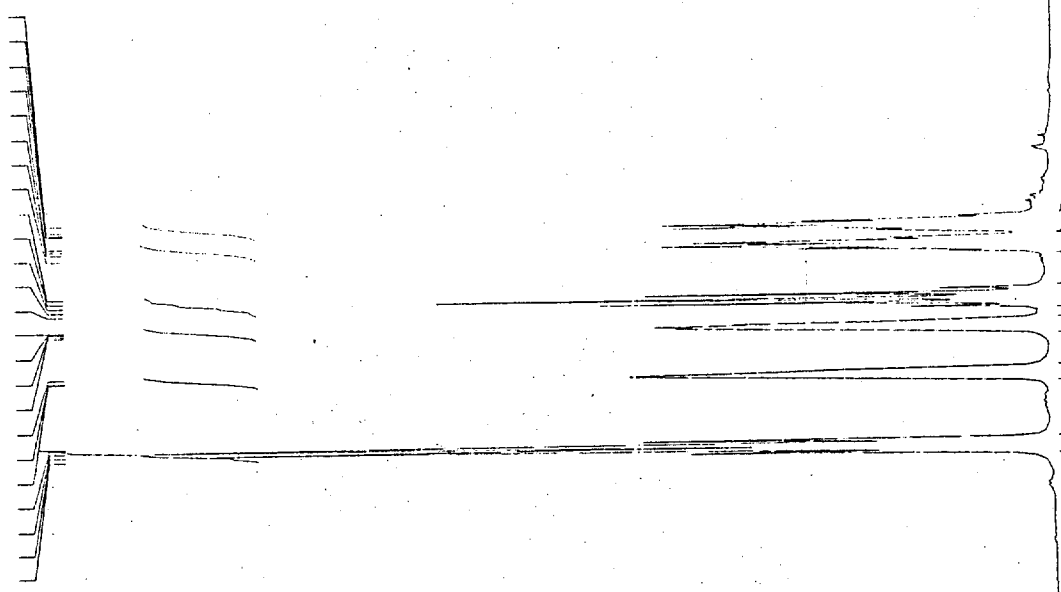


Table 1, Compound 8



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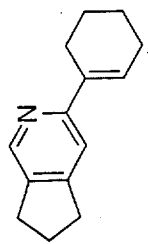
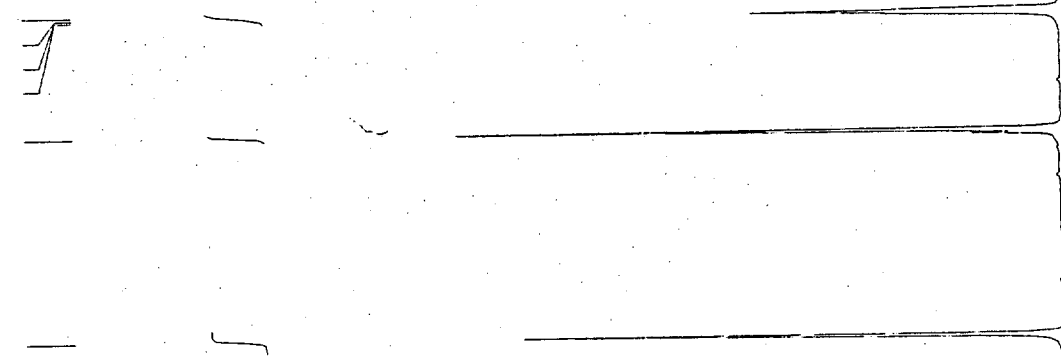


Table 1, Compound 10

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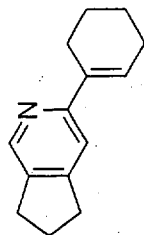
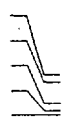


Table 1, Compound 10

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136.898
127.455
115.222

$\pi\pi$



ppm

20

40

60

80

100

120

140

160

180

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