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of Reliable Methods
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of Organic Compounds

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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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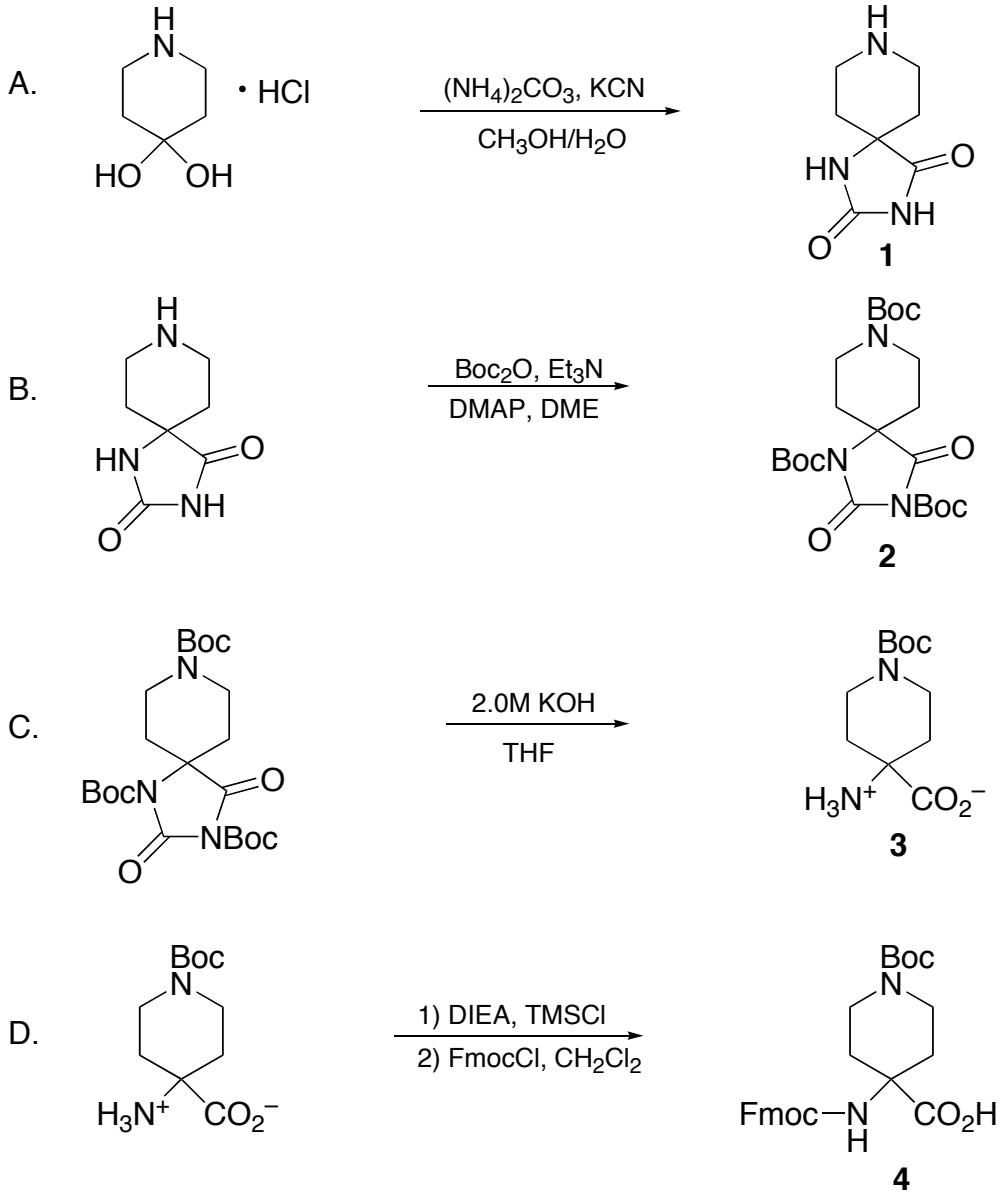
A CONVENIENT PREPARATION OF AN ORTHOGONALLY PROTECTED C^{α},C^{α}-DISUBSTITUTED AMINO ACID ANALOG OF LYSINE: 1-*tert*-BUTYLOXYCARBONYL-4-((9-FLUORENYLMETHYLOXYCARBONYL)AMINO)-PIPERIDINE-4-CARBOXYLIC ACID

[1,4-Piperidinedicarboxylic acid, 4-[[(9*H*-fluoren-9-ylmethyloxy)carbonyl]amino]-, (1,1-dimethylethyl) ester]



Submitted by Lars G. J. Hammarström, Yanwen Fu, Sidney Vail, Robert P. Hammer, and Mark L. McLaughlin.[1]
Checked by Rick L. Danheiser and Martin E. Hayes.

1. Procedure

Caution: Potassium cyanide is a potent poison, which should always be handled with gloves in a well-ventilated hood. Contact with acid releases toxic hydrogen cyanide gas.

A. Piperidine-4-spiro-5'-hydantoin (**1**). A 1000-mL, single-necked, round-bottomed flask equipped with a magnetic stirbar and an addition funnel fitted with an argon inlet is charged with 4-piperidone monohydrate hydrochloride (30.0 g, 195 mmol), ammonium carbonate (41.3 g, 420 mmol), 250 mL of methanol, and 150 mL of deionized water (Note 1). The mixture is allowed to stir at room temperature until all solids dissolve and then a solution of potassium cyanide (26.7 g, 410 mmol) (Note 2) in 100 mL of deionized water is added dropwise to the reaction mixture over 10 min. The reaction flask is sealed with a glass stopper and the reaction mixture is stirred at room temperature for 48 h. The resulting suspension is concentrated to a volume of 300 mL by rotary evaporation at 40 °C, after which the solution is cooled to 10 °C. The white solid which precipitates is collected in a Büchner funnel using suction filtration. Concentration of the filtrate to a volume of 200 mL results in precipitation of additional product that is separated by filtration and combined with the first crop. The resulting light yellow solid is washed with four 25-mL portions of deionized water to yield a white solid (Note 3). The product is allowed to dry for 2 h in the air and then is dried under reduced pressure (85 °C; 0.5 mm) for 48 h (Note 4) to yield 25.7-26.2 g (77-79%) of the desired hydantoin as a white solid (Note 5).

*B. 1-tert-Butyloxycarbonylpiperidine-4-spiro-5'-(1',3'-bis(tert-butyloxy-carbonyl)) hydantoin (**2**).* A 2000-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, glass stopper, and an overhead mechanical stirrer is charged with a suspension of the hydantoin **1** (26.0 g, 154 mmol) in 1000 mL of 1,2-dimethoxyethane (Note 6). Triethylamine (15.7 g, 154 mmol) (Note 7) is added in one portion, and the resulting white suspension is stirred for 30 min. Di-*tert*-butyl dicarbonate (168.0 g, 770 mmol) is then added by pipette, followed by 4-dimethylaminopyridine (DMAP) (0.2 g, 1.5 mmol) (Note 8). Six additional 0.2 g-portions of DMAP are added at 12 h intervals during the course of the reaction. The reaction mixture is stirred vigorously for a total of 72 h, and the resulting light yellow solid is then collected in a Büchner funnel using suction filtration. The filtrate is concentrated to a volume of 60 mL by rotary evaporation, and the resulting solution is cooled to 15 °C. The precipitate which appears is collected using suction filtration, added to the first crop, and the combined solids are dissolved in 500 mL of chloroform. This solution is washed with three 200-mL portions of 1.0N HCl, and the combined aqueous phases are extracted with 100 mL of chloroform. The combined organic layers are washed with 100 mL of saturated aq $NaHCO_3$ solution and 100 mL of brine (Note 9), dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. The resulting solid is dried at room temperature at 0.01 mm for 24 h. The resulting finely ground light yellow solid is suspended in 400 mL of diethyl ether in a 1000-mL, round-bottomed flask equipped with a magnetic stirbar, stirred for 2 h, and filtered on a Büchner funnel washing with four 50-mL portions of diethyl ether (Note 10). The product is dried under vacuum (85 °C; 0.5 mm) for 24 h to give 60.0–65.3 g (83-90%) of **2** as a ivory-colored solid (Note 11).

C. 4-Amino-1-tert-butyloxycarbonylpiperidine-4-carboxylic acid (**3**). A 2000-mL, round-bottomed flask equipped with a magnetic stirbar is charged with a suspension of the hydantoin **2** (40.0 g, 0.8 mol) in 340 mL of THF (Note 12), and 340 mL of 2.0M potassium hydroxide solution (Note 13) is added in one portion. The flask is stoppered and the reaction mixture is stirred for 4 h (Note 14) and then poured into a 1000-mL separatory funnel. The layers are allowed to separate over 45 min and the aqueous layer is then drained into a 1000-mL round-bottomed flask. This solution is cooled at 0 °C while the pH is adjusted to 8.0 by the slow addition of ca. 100

mL of 6.0N HCl solution. The resulting solution is further acidified to pH 6.5 by slow addition of 2.0 N HCl solution (Note 15). The white precipitate which appears is collected by filtration on a Büchner funnel and the filtrate is concentrated to a volume of 60 mL to furnish additional precipitate which is collected by filtration. The combined portions of white solid are dried at room temperature under reduced pressure (65 °C; 0.5 mm) for 12 h and then suspended in 100 mL of chloroform (Note 16) and stirred for 45 min. The white solid is filtered and then dried under reduced pressure (85 °C; 0.5 mm) for 24 h to yield 13.4–14.1 g (64-68%) (Note 17) of the amino acid **3** as a white solid (Note 18).

D. 1-tert-Butyloxycarbonyl-4-(9-fluorenylmethyloxycarbonylamino) piperidine-4-carboxylic acid (**4**). A 1000-mL, three-necked, round-bottomed flask is equipped with a magnetic stirbar, argon inlet adapter, rubber septum, and an exit tube submerged in a 6.0M KOH solution. The apparatus is flame-dried under a flow of argon and then charged with finely ground amino acid **3** (17.0 g, 69.6 mmol). Anhydrous dichloromethane (500 mL) is added, followed by diisopropylethylamine (22.5 g, 30.3 mL, 174 mmol) which is added via syringe over 10 min (Note 19). The reaction mixture is stirred for 30 min and then chlorotrimethylsilane (15.1 g, 17.6 mL, 140 mmol) (Note 20) is added dropwise over 6 min (Note 21). After 30 min, the septum is replaced with a condenser and the reaction mixture is heated at reflux for 3 h during which time the mixture becomes homogeneous. At 30 min intervals, the reaction vessel is flushed with argon for 30 sec to remove HCl formed in the reaction. The solution is then cooled to –10 °C and 9-fluorenylmethyl chloroformate (Fmoc-Cl) (16.7 g, 64.6 mmol) (Note 22) is added in one portion. The resulting solution is stirred for 3 h under a constant slow stream of argon and then concentrated by rotary evaporation. The resulting paste is taken up in 400 mL of diethyl ether and 1000 mL of aqueous 2.5% Na_2CO_3 solution (Note 23), and the aqueous layer is separated (Note 24) and washed with two 100-mL portions of ether. The

aqueous layer is transferred to a 1-L beaker and cooled in an ice bath while 2.0N HCl is added to adjust the pH to 2.0. The resulting suspension is transferred to a 2-L separatory funnel (Note 25), and the precipitated acid is extracted with one 300-mL portion and two 150-mL portions of ethyl acetate. The combined organic phases are dried over $MgSO_4$, filtered, and concentrated by rotary evaporation and then at 60 °C under reduced pressure (0.5 mm) for 10 h. The resulting light yellow solid is suspended in 200 mL of hexane, stirred for 45 min, and then collected by filtration on a Büchner funnel (Note 26). The product is dried under reduced pressure (60 °C; 0.5 mm) for 24 h to afford 22.0–24.4 g (73-76%) (Note 27) of the desired product **4** (Note 28) as a white solid.

2. Notes

1. 4-Piperidone monohydrate hydrochloride and ammonium carbonate were purchased from Alfa-Aesar Chemical Company and used without further purification. Methanol was purchased from Mallinckrodt Chemical Company and used as received.

2. Potassium cyanide was purchased from Alfa Aesar Chemical Company and used without further purification.

3. Precipitated hydantoin must be washed with sufficient water to remove any residual ammonia, which can interfere with subsequent reactions. If an ammonia odor or yellow color persists after the initial water washes, additional washes should be performed.

4. The submitters dried their product in a vacuum oven for 8 h, then ground the resulting solid to a fine powder and returned it to the oven for 40 h further.

5. The hydantoin **1** is only slightly soluble in CD_3SOCD_3 and displays the following spectroscopic properties: ^{1}H NMR (500 MHz, CD_3SOCD_3) δ: 1.37 (d, *J* = 12.5 Hz, 2 H), 1.68 (dt, *J* = 4.6, 12.2 Hz, 2 H), 2.64 (app t, *J* = 12 Hz, 2 H), 2.83 (app d, *J* = 12.2 Hz, 2 H), 8.47 (s, 1 H), 10.3-10.6 (s, 2 H). ^{13}C NMR (125 MHz, CD_3SOCD_3) δ: 33.8, 41.2, 61.1, 156.4, 178.1.

6. 1,2-Dimethoxyethane (Dri-Solv) was purchased from EM Science Chemical Company and used as received.

7. Triethylamine was purchased from Alfa-Aesar Chemical Company and used without further purification.

8. Di-*tert*-butyl dicarbonate and 4-dimethylaminopyridine were purchased from Alfa-Aesar Chemical Company and used without further purification.

9. The initial HCl wash results in an emulsion and up to 2 h may be required for phase separation. At that point, any remaining emulsion should be separated and added to 100 mL of chloroform and 100 mL of 1.0N HCl solution. The chloroform layer is then combined with the other organic phases.

10. Triturating with diethyl ether was found to be necessary to successfully remove residual di-*tert*-butyl dicarbonate and di-*tert*-butyl

iminodicarboxylate which may be produced as a result of residual traces of ammonia from step A.

11. Spectroscopic data for **2**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.46 (s, 9 H), 1.53 (s, 9 H), 1.57 (s, 9 H), 1.73 (m, 2 H), 2.67 (dt, *J* = 5.2, 13.6 Hz, 2 H), 3.32-3.50 (m, 2 H), 4.00-4.23 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.9, 28.2, 28.6, 29.7, 29.9, 39.2, 40.2, 62.5, 80.1, 85.3, 87.1, 145.2, 147.3, 148.0, 154.5, 169.8.

12. Tetrahydrofuran was purchased from Mallinckrodt Chemical Company and used as received.

13. Potassium hydroxide was purchased from Mallinckrodt Chemical Company and used without further purification.

14. Two phases appear within the first 15 min due to the heavy ionic content of the aqueous layer. Di-*tert*-butyl iminodicarboxylate, which is produced as a result of the hydrolysis, is selectively soluble in the THF layer, while the amino carboxylate salt of the product remains in solution in the aqueous layer.

15. Reaching the equilibrium where the amino acid zwitterion predominates is a slow process. After acidifying to pH 6.5, the solution is allowed to stir at 0 °C for 25 min during which time the pH of the solution slowly increases. The pH is readjusted to pH 6.5 by slow addition of 2.0N HCl at 0 °C. Repetition of this procedure as many as ten times may be necessary to insure the pH value of the aqueous solution remains at 6.5. Triturating with chloroform is necessary to successfully remove a trace amount of 1-*tert*-butyloxycarbonylpiperidine-4-spiro-5'-(1'-*tert*-butyloxy-carbonyl)-hydantoin.

16. The submitters report obtaining **3** in 87% yield.

17. Compound **3** is only slightly soluble in MeOH-d_4. Spectroscopic data for **3**: ^{1}H NMR (500 MHz, CD_3OD) δ: 1.44 (s, 9 H), 1.58-1.66 (m, 2 H), 2.07-2.14 (m, 2 H), 3.44-3.54 (m, 2 H), 3.64-3.72 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.8, 33.3, 40.7, 41.7, 59.9, 81.5, 156.5, 175.9.

18. Diisopropylethylamine was purchased from Alfa-Aesar chemical Company and used without further purification. Dichloromethane was purified by pressure filtration through activated alumina.

19. Chlorotrimethylsilane was distilled from calcium hydride immediately prior to use.

20. Upon addition of chlorotrimethylsilane, vigorous HCl production is observed.

21. The checkers purchased Fmoc-Cl from Alfa-Aesar Chemical Company. Impurities are sometimes found in Fmoc-Cl purchased from various sources, and it is necessary to verify its purity by TLC and ^{1}H-NMR analysis. If necessary, Fmoc-Cl can be purified by recrystallization from hexane.

22. Efficient magnetic stirring for up to 2 h is necessary to dissolve the crude product in the mixture of ether and aqueous 2.5% sodium carbonate solution.

23. The solution is allowed to stand in a separatory funnel for at least 30 min before the aqueous layer is drained out. It is sometimes observed that a portion of the sodium carboxylate salt of **4** forms a third layer below the aqueous layer, in which case this layer should be combined with the sodium carbonate layer.

24. The precipitated amino acid forms a gum on the inside walls of the beaker. Magnetic stirring and manual agitation with excess ethyl acetate is necessary to transfer the residual precipitate.

25. Triturating with hexane is necessary to remove trace amounts of solvents (ethyl acetate and ether) in the product.

26. The submitters obtained 26.9 g (83%) of the product.

27. The product displays the following spectroscopic data: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.46 (s, 9 H), 1.90-2.12 (br s, 4 H), 3.00-3.13 (br s, 2 H), 3.72-3.92 (br s, 2 H), 4.16-4.22 (m, 1 H), 4.38-4.48 (br s, 2 H), 5.06-5.14 (br s, 1 H), 7.30 (t, J = 7.4 Hz, 2 H), 7.39 (t, J = 7.4 Hz, 2 H), 7.56 (d, J = 7.0 Hz, 2 H), 7.75 (d, J = 7.4 Hz, 2 H). ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ: 28.1, 31.3, 46.7, 56.7, 65.4, 78.8, 120.2, 125.3, 127.1, 127.7, 140.8, 143.8, 153.9, 155.4, 175.1.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The effect of C^{α},C^{α}-disubstituted amino acids ($\alpha\alpha$AAs) on peptide secondary structure has been studied in recent years.[2a-d] While longer side-chain C^{α},C^{α}-di-*n*-alkyl amino acids promote extended peptide conformation,[2a] alicyclic $\alpha\alpha$AAs, in which the C^{α} carbon forms a cyclic bridge with itself, such a 1-aminocyclopentane-1-carboxylic acid (Ac_5c) and 1-aminocyclohexane-1-carboxylic acid (Ac_6c), have helix-forming characteristics similar to those of 1-aminoisobutyric acid (Aib).[2a,c]

Since most $\alpha\alpha$AAs are hydrophobic in nature, peptides rich in $\alpha\alpha$AAs are generally restricted to study in organic solvents due to their low solubility in aqueous media. There have been very few examples of side-chain functionalized $\alpha\alpha$AAs that would allow for the synthesis of highly water-soluble peptides rich in $\alpha\alpha$AA content.[3] This is primarily due to difficulty of synthesis, since side-chain functionalized derivatives must be orthogonally protected to allow for incorporation into solid-phase peptide synthesis. The harsh conditions, under which standard methods of $\alpha\alpha$AA synthesis are performed, make this a difficult task.

Despite recent advances in synthetic methods to mildly generate polyfunctional ααAAs,[4] the Bucherer-Berg approach is still the most convenient method to generate simple ααAAs in good yields.[5] However, hydantoins suffer from the limitation of requiring harsh conditions for hydrolysis, thus compromising the ability to generate side-chain protected polyfunctional amino acids. This problem was partially overcome by Rebek and coworkers, who discovered that *N,N′*-bis-(*t*-butyloxycarbonyl)-hydantoins can be hydrolyzed under much milder conditions.[6] The progress made in ααAA synthesis by mild hydantoin hydrolysis allowed the submitters to develop the synthesis of the orthogonally protected ααAA Fmoc-Api(Boc)-OH. This ααAA analog of lysine allows for the preparation of alicyclic ααAAs, while retaining high water-solubility.[6] As with other alicyclic ααAAs, Api has been found to strongly favor helical conformations of resulting peptides.[7b]

It has been found that the *tris*(*tert*-butyloxycarbonyl) protected hydantoin of 4-piperidone **2**, selectively hydrolyses in alkali to yield the *N*-*tert*-butyloxycarbonylated piperidine amino acid **3**. The hydrolysis, which is performed in a biphasic mixture of THF and 2.0M KOH at room temperature, cleanly partitions the deprotonated 4-amino-*N′*-(*tert*-butyloxycarbonyl)piperidine-4-carboxylic acid into the aqueous phase of the reaction with minimal contamination of the hydrolysis product, di-*tert*-butyl iminodicarboxylate, which partitions into the THF layer. Upon neutralization of the aqueous phase with aqueous hydrochloric acid, the zwitterion of the amino acid is isolated. The Bolin procedure to introduce the 9-fluorenylmethyloxycarbonyl protecting group efficiently produces **4**.[8] This synthesis is a significant improvement over the previously described method[9] where the final protection step was complicated by contamination of the hydrolysis side-product, di-*tert*-butyl iminodicarboxylate, which is very difficult to separate from **4**, even by chromatographic means.

1. Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803.

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

4-Piperidone monohydrate hydrochloride: 4-Piperidinone, hydrochloride; (41979-39-9).

Ammonium carbonate: Carbonic acid, diammonium salt; (506-87-6).

Potassium cyanide: Potassium cyanide [K(CN)]; (151-50-8)

Piperidine-4-spiro-5'-hydantoin: 1,3,8-Triazaspiro [4.5]decane-2,4-dione; (13625-39-3).

Triethylamine: Ethanamine, *N,N*-diethyl; (121-44-8).

Di-*tert*-butyl dicarbonate: Dicarbonic acid, bis(1,1-dimethylethyl) ester; (24424-99-5).

DMAP(4-(Dimethylamino)pyridine: 4-Pyridinamine, N,N-dimethyl-; (1122-58-3).

1-*tert*-Butyloxycarbonylpiperidine-4-spiro-5'-(1',3'-bis(*tert*-butyloxycarbonyl) hydantoin: 1,3,8-Triazaspiro[4.5]decane-1,3,8-tricarboxylic acid, 2,4-dioxo-, tris(1-dimethylethyl) ester; (183673-68-9).

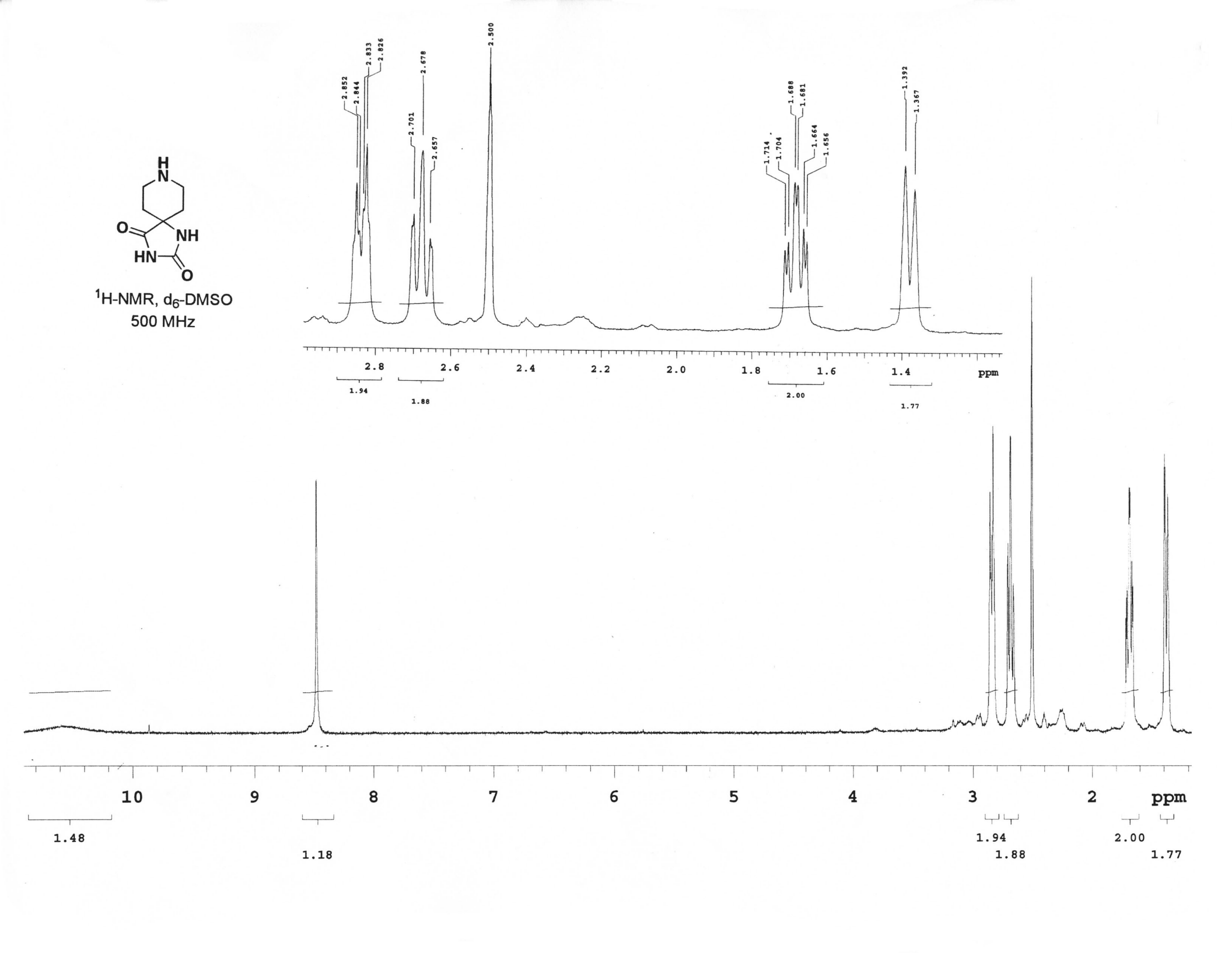
4-Amino-1-*tert*-butyloxycarbonylpiperidine-4-carboxylic acid: 1,4-Piperidinedicarboxylic acid, 4-amino-, 1-(1,1-dimethylethyl) ester; (183673-71-4).

1-*tert*-Butyloxycarbonyl-4-(9-fluorenylmethyloxycarbonylamino)piperidine-4-carboxylic acid: 1,4-Piperidinedicarboxylic acid, 4-[[(9H-fluoren-9-ylmethyloxy)carbonyl]amino]-,1-(1,1-dimethylethyl) ester; (183673-66-7).

Diisopropylethylamine: 2-Propanamine, *N*-ethyl-*N*-(1-methylethyl)-; (7087-68-5).

9-Fluorenylmethyl chloroformate: Carbonochloridic acid, 9H-fluoren-9-ylmethyl ester; (28920-43-6).

Chlorotrimethylsilane: Silane, chlorotrimethyl-; (75-77-4).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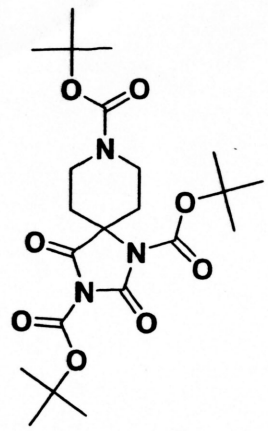

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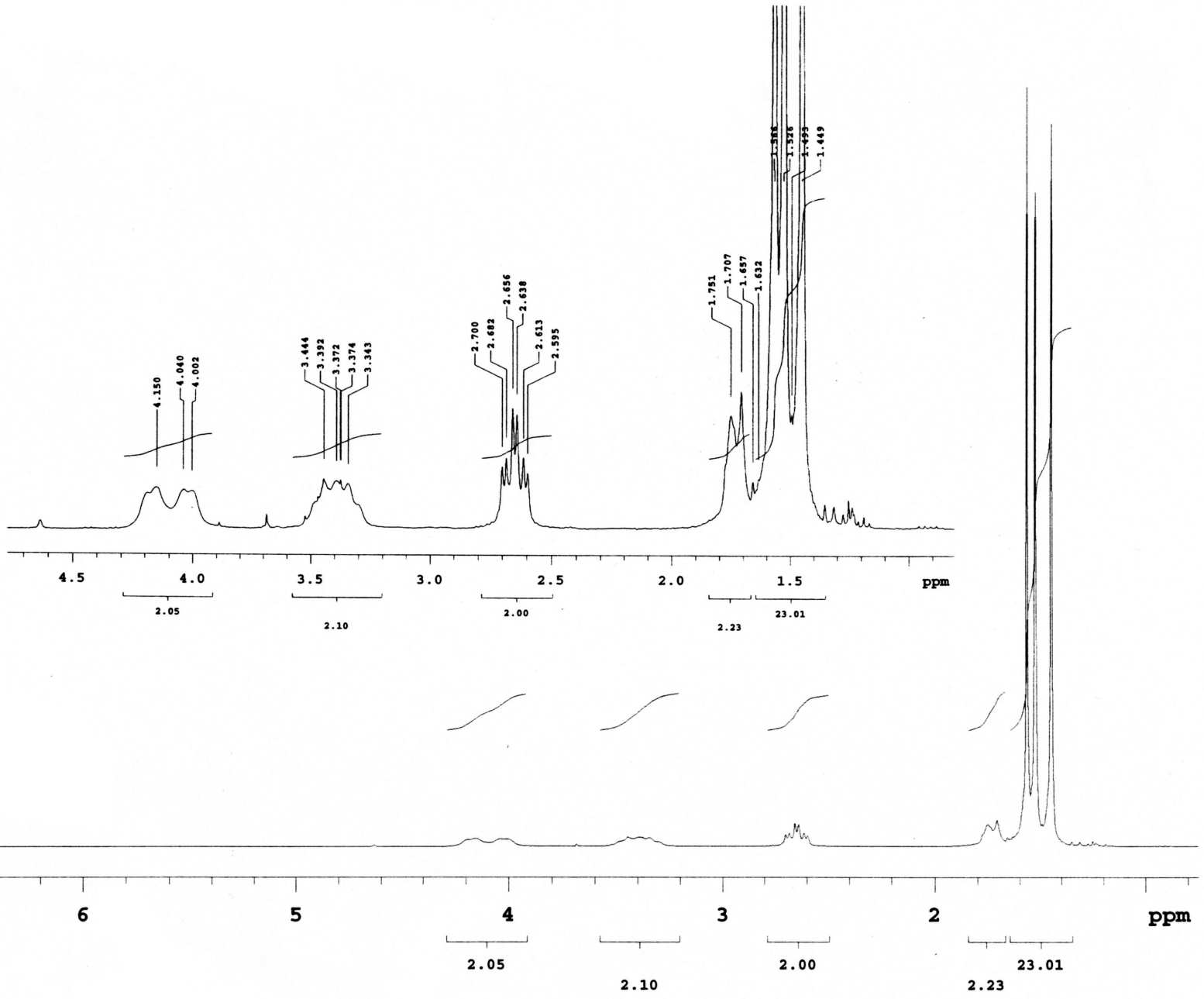

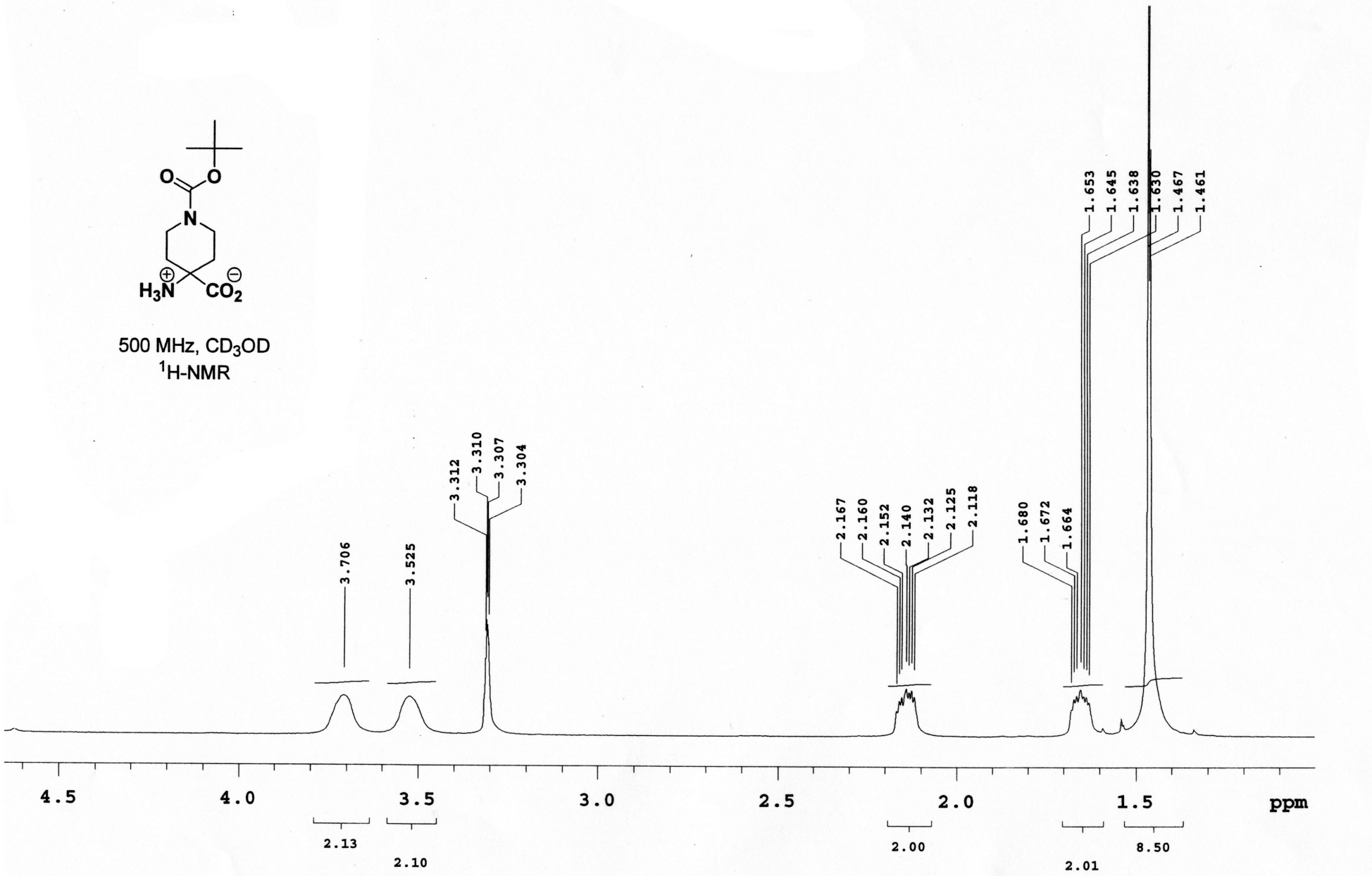
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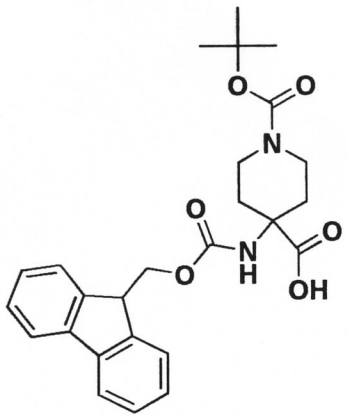

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