Unusual Oxidative Purine-to-Imidazo[1,5-*c*]imidazole Ring Transformation

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SUPPORTING INFORMATION

Experimental Section

Materials. Solvents, reagents and deuterated solvents were from Aldrich and were dried over 4 A molecular sieves. Glacial acetic acid was purified by fractional distillation, and fraction bp 118°C was used in chlorination reactions. Dry methanol and ether were prepared by conventional distillation over magnesium turnings or sodium wire. Chlorine was dried by passing through concentrated H_2SO_4 and a drying tube containing anhydrous $CaCl_2$.

General. Melting points were determined with a Kofler microscope and are corrected. Infrared spectra (in cm^{-1}) were taken on a Perkin-Elmer FT-IR 1725X spectrometer as KBr disks. The ^1H- and ^{13}C-NMR spectra were recorded in DMSO-d_6, unless stated otherwise, with a Bruker Avance 600 (^1H, 600 MHz; ^{13}C, 150 MHz) instrument. Chemical shifts are given in δ units (ppm) from internal TMS and coupling constants are expressed in Hz (br broad, s singlet, d doublet, t triplet, q quartet); multiplicities in ^{13}C spectra were determined by off-resonance decoupling. Mass spectra were measured on a Micromass AutoSpecQ instrument at 70eV, 150 μA, 200°; *m/z* values are given with relative intensities (%) in parentheses.

Chlorination of 3,9-dimethyluric acid (1). A continuous stream of chlorine was passed through the suspension of finely powdered 3,9-dimethyluric acid (**1**, 10g, 50 mmol) in dry acetic acid (10 mL), according to Biltz's procedure.[1] Reaction mixture was purged with dry argon to give tiny colorless needles on standing. The crystalline end-product has been originally assigned as 4,5-dichloro-3,9-dimethyltetrahydropurine-2,6,8-trione (**III**), and the revised structure, 7a-chloro-6-methyl-7-methyliminodihydroimidazo[1,5-*c*]imidazole-1,3,5-trione hydrochloride (**5**), is now formulated for this compound. Crystallization of this product is slowed considerably, or even quenched, in the presence of moisture. Compared with the previously reported product, which analyzed for an acetic acid hemi-solvate, our sample ground to a fine powder, was dried in a high vacuum (10^{-5} Torr) for several days that effectively removed acetic acid from an initially formed crystalline solvate (9.5-10.9 g, 70-89%). The product was hygroscopic and cannot be recrystallized unchanged. Furthermore, we found it impossible to cause any reaction to take place with dry methanol, a behavior clearly incompatible with above assignment; mp 308-310° dec (lit[1] mp 260-270° dec); IR: 3300-3050 (NH), 1828, 1780-1680 (CO) cm^{-1}; NMR spectra were not measured owing to very low solubility and decomposition.

Anal. Calcd. For $C_7H_8Cl_2N_4O_3$: C, 31.48; H, 3.02; Cl, 26.55; N, 20.98. Found: C, 31.66; H, 3.38; Cl, 26.24; N, 20.61.

A flocculent, ill-defined acetic acid solvate, which shows no definite mp could be obtained immediately after reaction of **1** with chlorine by precipitation with dry ether and subsequent drying in a high vacuum. Unstable product, which could not be purified by crystallization, was originally formulated as 4-chloro-3,9-dimethyl-4,9-dihydro-3*H*-purine-2,6,8-trione (**II**). Attempts to obtain its NMR spectra were unsuccessful due to extensive decomposition in all usual solvents. On treatment with dry acetic acid saturated with hydrogen chloride this could be converted, albeit in lower yields, to the normal end products of chlorination, the crystalline product **5** and 1,7-dimethylspirodihydantoin (**6**), as confirmed by comparison of IR spectra with authentic samples.

1,7-Dimethylspirodihydantoin (6). Concentration of the mother liquor after isolation of **5** yielded the by-product **6**, obtained as colorless plates (0.5-1.1g, 5-10%) on recrystallization from water; mp 264° (lit[1,2] mp 264-265°); ^{1}H NMR: δ 11.38 (s), 8.78 (s), 2.97 (s), 2.75 (s); ^{13}C NMR: δ 168.6 (s), 166.1 (s), 156.4 (s), 155.3 (s), 79.4 (s), 25.7 (q), 25.4 (q).

***cis*-4,5-Dimethoxy-3,9-dimethyltetrahydropurine-2,6,8-trione (3c).** Upon treatment with dry methanol (-15°), the unstable product (3 g), originally assigned as 4-chloro-3,9-dimethyl-4,9-dihydro-3*H*-purine-2,6,8-trione II,[1] gave variable yields of **6c** (0.3-1.3 g) as colorless prisms (methanol); mp 222° dec (lit[3] mp 222-223° dec).

Reductive dechlorination to 6-methyl-7-methylamino-6*H*-imidazo[1,5-*c*]imidazole-1,3,5-trione (**7**). In accordance with the original procedure,[1] the reaction of compound **5** (10 g), erroneously formulated as **III**, with potassium iodide (8 g) and sodium thiosulfate decahydrate (12 g) in water (25 mL) gave fine clustered needles (3-4 g) of the product previously formulated as 3,9-dimethyl-4,9-dihydro-3*H*-purine-2,6,8-trione (**IV**), but this is factually the 6-methyl-7-methylamino-6*H*-imidazo[1,5-*c*]imidazole-1,3,5-trione (**7**). It showed the same mp 416-420° dec as 3,9-dimethyluric acid (**1**) and there is no lowering when they are mixed. Upon brief heating at 310-315°, or in refluxing acetic acid (10 min), **7** underwent virtually quantitative transformation into 3,9-dimethyluric acid (**1**). Low solubility in all usual solvents precluded a thorough NMR spectroscopic characterization of this product; IR: 3279, 3181 (NH) 1795, 1703, 1695, 1682 (CO) 1653, 1642, 1632; ^{1}H NMR (TFA-*d*): δ 3.82 (s, NMe), 3.46 (s, NMe); ^{13}C NMR (TFA-*d*): δ 163.1 (s), 160.8 (s), 151.5 (s), 150.2 (s), 62.2 (s), 34.1 (q), 28.0 (q). NMR spectra in DMSO-d_6 and D_2SO_4 are shown in Figures S1-S3 (see also [7a-^{13}C]-**7**, p. SI - 3).

Conversion of 7 into 5 with chlorine. Chlorination of 6-methyl-7-methylamino-6*H*-imidazo[1,5-*c*]imidazole-1,3,5-trione (**7**, 1.96 g, 10 mmol) for 1-2 min, in either dry methanol* (10 mL) at -20°C or in acetic acid (2 mL) at room temperature, on removal of chlorine and drying crystals in a high vacuum, gives back the dichloro compound **5** (1.9 g, 71% and 2.2 g, 82%, respectively). IR spectra confirmed identity of these samples with **5** obtained by chlorination of 3,9-dimethyluric acid (**1**).

Anal. Calcd. For $C_7H_8Cl_2N_4O_3$: C, 31.48; H, 3.02; Cl, 26.55; N, 20.98. Found: C, 31.40, 31.71; H, 3.40; Cl, 26.33, 26.22; N, 20.67, 20.75.

** CAUTION! Methanolic reaction mixture may ignite, possibly resulting in an explosion, due to crystal deposition and local overheating. Therefore, the inlet tube must be at least 5 mm above the bottom of the reaction vessel and all safety precautions must be rigorously applied.*

2-Methylimidazo[1,5-*c*]imidazole-1,3,5,7-tetraone (8). 6-Methyl-7-methylamino-6*H*-imidazo[1,5-*c*]imidazole-1,3,5-trione (**7**, 1.96 g, 10 mmol) was dissolved in aqueous hydrochloric acid (20 mL, 4 *N*). The crystalline product which separated on standing was recrystallized from ethanol to give colorless prisms (**8**, 1.5 g, 82%); mp 261-262° dec (lit[1] mp 262° dec); IR: 3336 (NH), 2914 (CH), 1775, 1770, 1760, 1755, 1746, 1712 (CO); MS: *m/z* 183 (M+, 38), 140 (55), 126 (12), 113 (12), 97 (18), 83 (100), 69 (75), 57 (51); ^{1}H NMR: δ 11.60 (s, NH), 5.28 (s, CH), 2.77 (s, CH_3); ^{13}C NMR: δ 165.9 (d, C-1, $^{2}J_{CH}$ = 6.4), 165.0 (dd, C-7, $^{2}J_{CH}$ = 6.4, 3.3), 153.1 (s), 153.0 (s), 62.7 (d, $^{1}J_{CH}$ = 152), 25.4 (q). (*Cf.* Figures S4 – S6).

Decarboxylative decay of 8. While previous authors[1] have reported a single product, 1-carbamoyl-3-methylhydantoin (**9**, 74%), to be formed upon heating (100°C, 2.5 h) 2-methylimidazo[1,5-*c*]imidazole-1,3,5,7-tetraone (**8**, 2.2 g, 12 mmol) in water (150 mL), it is always possible to obtain a mixture of isomers separable by fractional crystallization from water.

1-Carbamoyl-3-methylhydantoin (9) was obtained as colourless plates (0.56-0.85g, 30-45%); mp 260-261° (lit[1] mp 250°); MS: *m/z* 157 (M^{+}, 100); IR: 3399, 3314 (NH_2), 1791, 1725, 1710 (CO); ^{1}H NMR: δ 7.52, 7,32 (ss, NH_2), 4.18 (s, CH_2), 2.88 (s, CH_3); ^{13}C NMR: δ 168.7 (s), 155.6 (s), 151.0 (s), 47.8 (t), 24.5 (q).

Anal. Calcd. for $C_5H_7N_3O_3$: C, 38.22; H, 4.49; N, 26.74. Found: C, 38.30; H, 4.61; N, 26.85.

1-Methylcarbamoylhydantoin (10) was obtained as colorless plates (0.66-0.75g, 35-40%); mp 255-256° dec; MS: *m/z* 157 (M^{+}, 88); IR: 3290, 3260 (NH), 1799, 1730, 1714 (CO); ^{1}H NMR: δ 11.45 (s, NH), 7,75 (q, NHMe, *J* = 4.6), 4.17 (s, CH_2), 2.74, (d, $NHCH_3$, *J* = 4.6); ^{13}C NMR: δ 169.9 (s), 156.0 (s), 151.3 (s), 49.1 (t), 26.3 (q).

Anal. Calcd. for $C_5H_7N_3O_3$: C, 38.22; H, 4.49; N, 26.74. Found: C, 38.09; H, 4.77; N, 26.58.

Attempted bromination of 3,9-dimethyluric acid (1). To a stirred suspension of finely powdered 3,9-dimethyluric acid (**1**, 10g, 50 mmol) in dry acetic acid (10 mL), freshly distilled bromine (20g, 6.5 mL, 130 mmol) was gradually added in the absence of light and moisture. No reaction can be observed even after stirring for 2 h at 25°C. The mixture was evaporated to dryness *in vacuo*. The orange-yellow residue was washed with an ice-cold 1% aqueous solution of $Na_2S_2O_3$, and then with water. Upon crystallization of its ammonium salt with charcoal, 3,9-dimethyluric acid (**1**, 9.6g) was recovered unchanged. The same results were obtained for a suspension of uric acid **1** in dry methanol (50 mL).

Syntheses and conversions of ^{13}C labeled compounds.

All compounds exhibited IR spectra almost identical with those of unlabeled compounds.

Synthesis of 3,9-dimethyl[5-^{13}C]uric acid ([5-^{13}C]-**1).** Dry, powdered dipotassium [5-^{13}C]urate[4] (417 mg, 1.7 mmol, 99%^{13}C) was heated with methyl tosylate (660 mg, 3.5 mmol) in *o*-dichlorobenzene (4 mL) for 7 hrs at 150°, according to the modified Biltz's procedure.[1] The crude product was in turn washed with *o*-dichlorobenzene, ether, neutralized with 1% aqueous acetic acid, washed, and dried. Recrystallization of its ammonium salt (with charcoal), acidification, and drying *in vacuo* yielded pure [5-^{13}C]-**1** (171 mg, 51%); ^{13}C NMR: δ 97.7 (s).

Chlorination of 3,9-dimethyl[5-^{13}C]urate ([5-^{13}C]-**1).** A stream of dry chlorine was passed through a suspension of finely powdered [5-^{13}C]-**1** (158 mg, 0.8 mmol) in dry acetic acid-d_4 (0.6 mL) under strictly anhydrous conditions. After all the solid had gone into solution (10 min), the mixture was purged with argon and transferred to a 5 mm NMR tube. Clear spectra were obtained in a short acquisition time. Initial spectrum showed only a broad ^{13}C signal at about 85.0 ppm with a barely resolved substructure, probably consisting of several peaks. This peak gradually decreases and new peaks appear, first after 20 min at 82.1 ppm, and then after *ca.* 1 h a smaller one at 79.3 ppm. Decay of the initial intermediate(s) was followed for 2 h, until the first crystals appeared (Figure 2). The broad peak at 85.0 ppm was still visible, and no other peaks are formed. Crystalline precipitate, which slowly deposited after the NMR experiment, was collected, washed with dry ether and dried *in vacuo* (10^{-5} Torr over KOH and P_2O_5, 40°, 4 days) to afford 7a-chloro-6-methyl-7-methylimino[7a-^{13}C]dihydroimidazo[1,5-*c*]imidazole-1,3,5-trione hydrochloride ([7a-^{13}C]-**5**, 170 mg, 79%) as tiny needles; mp 310-312° dec; ^{13}C NMR (AcOD-d_3): δ 81.5 ppm.

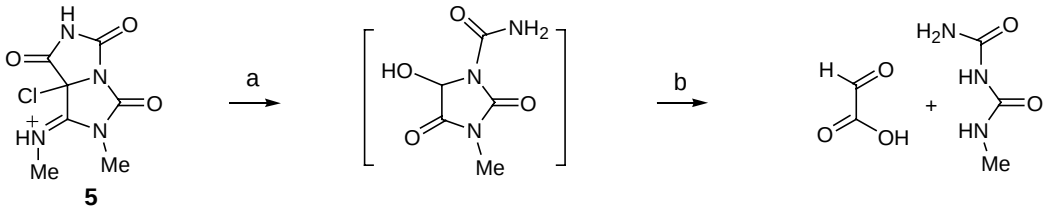
1,7-dimethyl[5-^{13}C]spirodihydantoin ([5-^{13}C]-**6).** This minor product was obtained upon concentration of the mother liquor and crystallization from water as small prisms (12 mg, 7%); mp 264°; ^{13}C NMR (AcOD-d_3): δ 79.4 (s) ppm.

6-Methyl-7-methylamino-6*H*-[7a-^{13}C]imidazo[1,5-*c*]imidazole-1,3,5-trione ([7a-^{13}C]-**7).** Reductive dechlorination was efficiently carried out in a chilled agate mortar by co-grinding potassium iodide (0.8 mmol), sodium thiosulfate (0.8 mmol), and 7a-chloro-6-methyl-7-methylimino[7a-^{13}C]dihydroimidazo[1,5-*c*]imidazole-1,3,5-trione hydrochloride ([7a-^{13}C]-**5**, 160 mg, 0.6 mmol) with water (0.3 mL, 1°C, 30 min). The product was collected, crystallized from boiling water (10 mL), and dried to give [7a-^{13}C]-**7** (52 mg, 44%) as fine needles, mp 415° dec; ^{13}C NMR (DMSO-d_6): δ 88.5 (s) and ^{13}C NMR (TFA-*d*): δ 59.7 (s). The TFA-*d* solution was evaporated to dryness and dried (10^{-5} Torr, KOH and P_2O_5, 2 h). The residue is then dissolved in DMSO-d_6 containing a touch of pyridine-d_5 to yield a signal at 88.2 (s) ppm assigned to the enediamine form of [7a-^{13}C]-**7**. A prolonged acquisition, owing to very low solubility in DMSO-d_6, gave unclean, but at this stage very important spectra of the unlabeled compound; ^{1}H NMR: δ 10.67 (brs, NH), 7.56 (brs, NH), 3.13 (s, NMe), 3.03 (s, NMe); ^{13}C NMR: δ 155.4, 146.8, 144.4, 141.2, 88.4, 32.2, 27.2. (*Cf.* Figures S1 and S2).

2-Methyl[7a-^{13}C]imidazo[1,5-*c*]imidazole-1,3,5,7-tetraone ([7a-^{13}C]-**8).** 6-Methyl-7-methylamino-6*H*-[7a-^{13}C]imidazo-[1,5-*c*]imidazole-1,3,5-trione ([7a-^{13}C]-**7**, 30 mg, 0.15 mmol) was dissolved in 4 *N* hydrochloric acid (0.3 mL) and prisms that separated were recrystallized from ethanol to yield [7a-^{13}C]-**8** (19 mg, 68%) as colorless prismatic crystals; mp 260-262° dec; ^{13}C NMR: δ 62.7 (d, $^1J_{CH}$ = 152).

Upon heating [7a-^{13}C]-**8** (9 mg) in water (0.6 mL, 100°, 1 h) and then evaporating to dryness, a mixture of 1-carbamoyl-3-methyl[5-^{13}C]hydantoin ([5-^{13}C]-**9**) and 1-methylcarbamoyl[5-^{13}C]hydantoin ([5-^{13}C]-**10**) was obtained and NMR spectrum was recorded without further purification; ^{13}C NMR: δ 49.1 (t, [5-^{13}C]-**9**), 47.8 (t, [5-^{13}C]-**10**).

Thermal rearrangement of [7a-^{13}C]-**7 to 3,9-dimethyl[5-^{13}C]uric acid (**[5-^{13}C]-**1).** Upon heating (310°, 10 min) in a sealed tube under argon dry 6-Methyl-7-methylamino-6H-[7a-^{13}C]imidazo[1,5-*c*]imidazole-1,3,5-trione ([7a-^{13}C]-**7**, 10 mg) rearranged to [5-^{13}C]-**1**; ^{13}C NMR: δ 97.7 (s).



5

Scheme S1. *asym*-Methylbiuret - a marker of new oxidative pathway; (a) H_2O (100°C); (b) OH^-.

Degradation of 5 to 1-methylbiuret and glyoxylic acid. 7a-Chloro-6-methyl-7-methyliminodihydroimidazo[1,5-*c*]imidazole-1,3,5-trione hydrochloride (**5**, 8.0 g, 30 mmol) was heated in water (50 mL) and when CO_2 evolution had ceased,[5] the solution was divided into two parts. To the first half was added a saturated aqueous soln of $Ba(OH)_2$ (150 mL) and allowed to stand overnight at room temperature. A large precipitate of barium salts was removed, the filtrate was then acidified with hydrochloric acid and evaporated to dryness *in vacuo*. The residue was finely ground and extracted with boiling ethanol (6 x 50 mL). The ethanolic extract was concentrated to yield 1-methylbiuret (1.2 g, 69%). The analytical sample was prepared after two recrystallizations from water as colourless prisms; mp 170-171°C (lit[6] mp 167-168°C); IR: 3420, 3392 (NH_2), 3310, 3285, 3245, 3185 (NH), 2885, 2805 (CH), 1685, 1605 (CO); ^{1}H NMR: δ 8.60 (s, NH), 7.35 (br, NHMe), 6.70 (s, NH_2), 2.62 (d, $NHCH_3$, J = 4.5); ^{13}C NMR: δ 159.7 (s, CO), 155.8 (s, CO), 24.8 (q, CH_3).

To the other half was added 20 mL of 2*N* NaOH and stirred for a half-hour. On treatment with a saturated solution of 2,4-dintrophenylhydrazine in 1*N* HCl (100 mL) this yielded orange-yellow prisms easy to identify as glyoxylic acid dintitrophenylhydrazone (2.0 g, 52%), mp 190-191°C dec (lit[7] 190°C dec), by both mixed melting point and IR spectroscopy.

References:

(1) Biltz, H.; Krzikalla, H., *Liebigs Annln Chem.* **1927**, *457*, 131-189.

(2) Biltz, H.; Krzikalla, H., *Liebigs Annln Chem.* **1921**, *423*, 255-281.

(3) Poje, N.; Poje, M. *Tetrahedron Lett.* **1995**, *36*, 8885-8886; Poje, N.; Palkovic, A.; Poje, M. *J. Heterocyclic Chem*. **1997**, *34*, 477-483.

(4) Modric, N.; Derome, A. E.; Ashcroft, S. J. H.; Poje, M. *Tetrahedron Lett.* **1992**, *33*, 6691-6694.

(5) Derivatives bearing a chloro or hydroxyl group in the 7a-position are susceptible to decarboxylation following the initial hydrolytic step in aqueous solutions. A crystalline product mp. 192-219°C dec separates on standing, was assigned as 1-carbamoyl-5-hydroxy-3-methylhydantoin (see ref. 1), but this is still an unresolved question. This substance can be crystallized from boiling water without decomposition, it is also stable to strong acids, but it is highly susceptible to base-catalyzed hydrolysis.

(6) Biltz, H.; Jeltsch, A. *Chem. Ber*. **1923**, *56*, 1914-1926.

(7) Weygand, F.; Bestmann, H. J. *Chem. Ber*. **1956**, *89*, 1912-1913.

Figure S1. ^{13}C NMR spectrum of **7** in DMSO-d_6

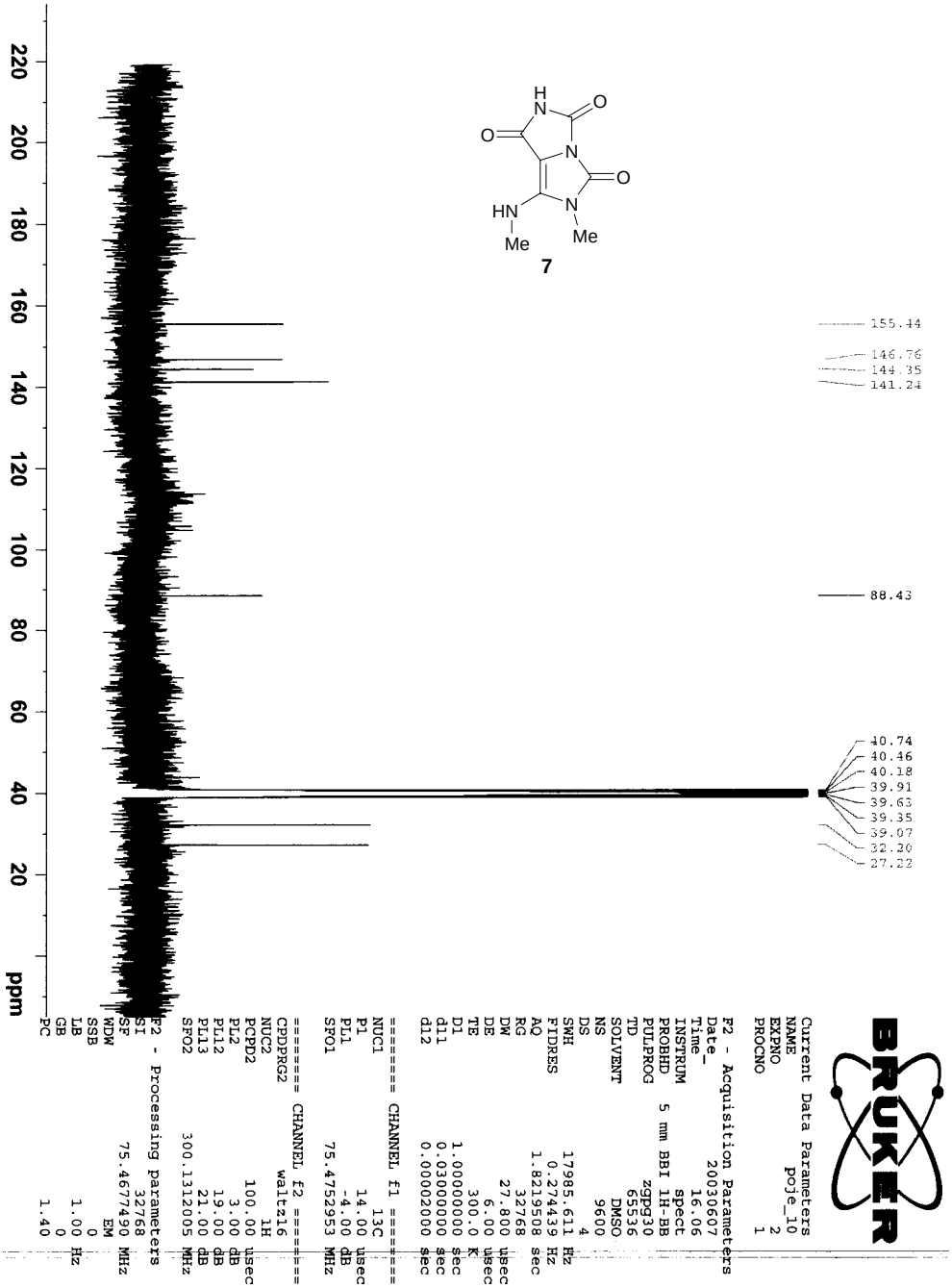


Figure S2. ^{1}H NMR spectrum of **7** in DMSO-d_6

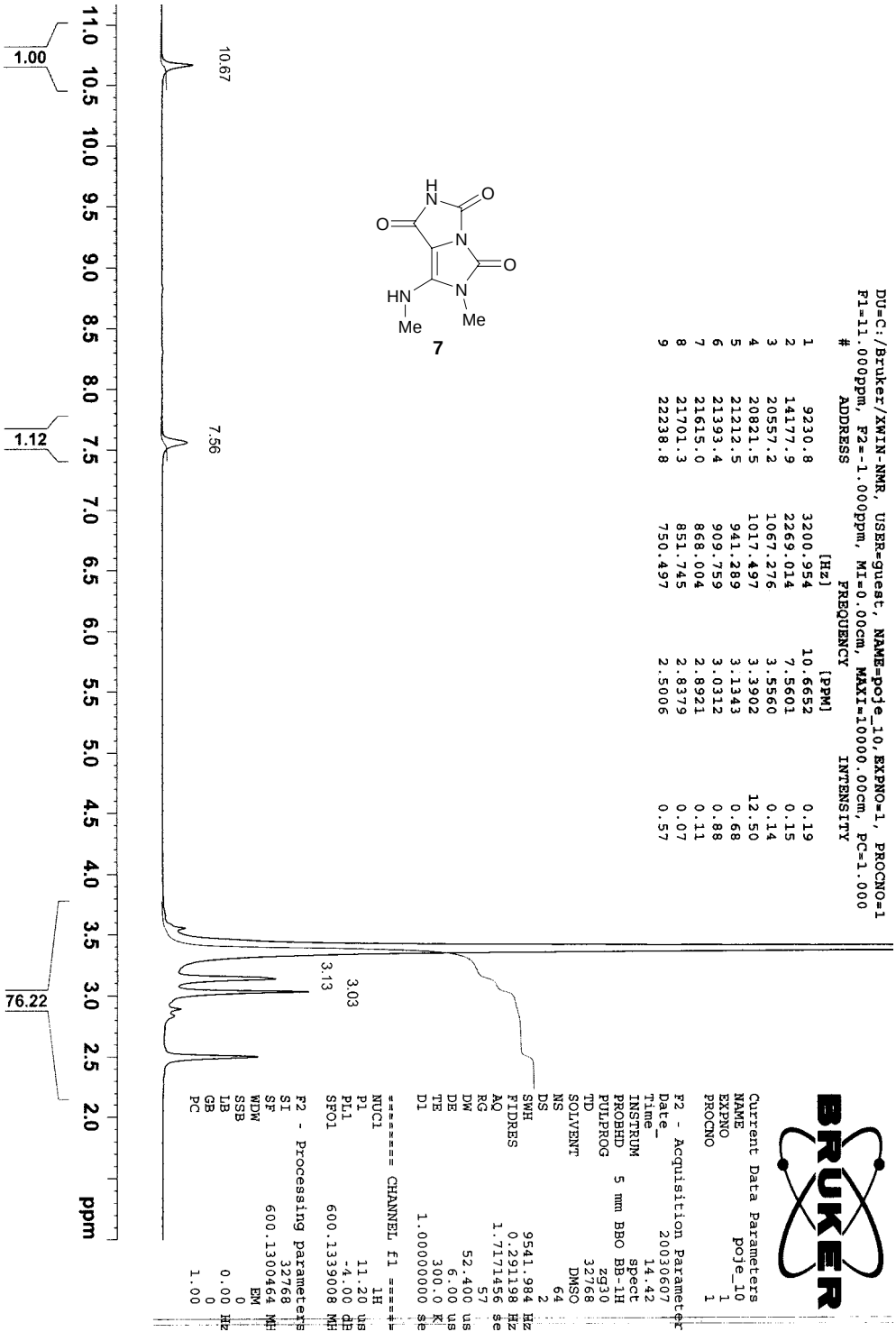


Figure S3. ^{13}C NMR spectrum of **7**-H^+ in D_2SO_4

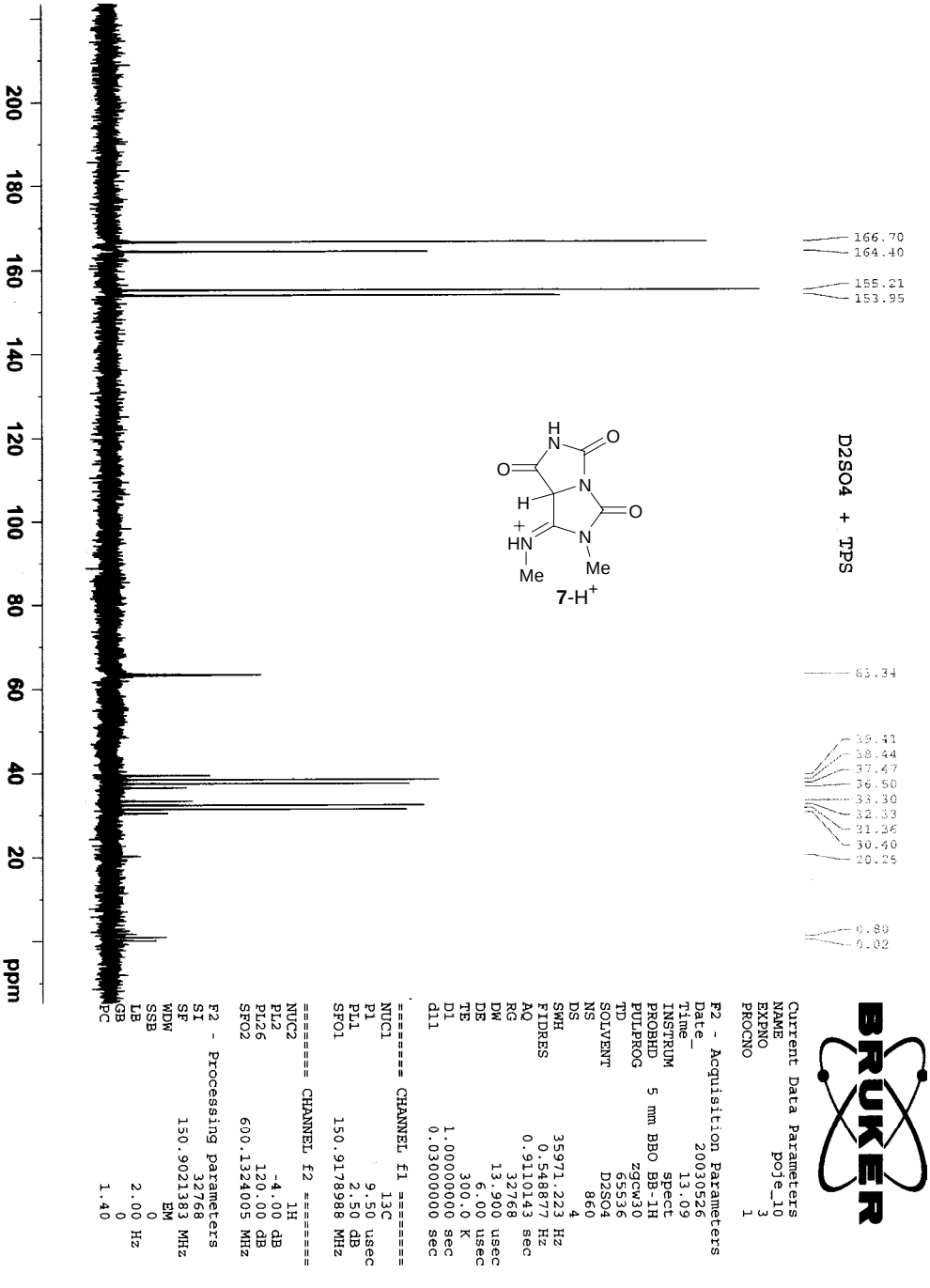


Figure S4a. ^{13}C NMR spectrum of **8** in DMSO-d_6

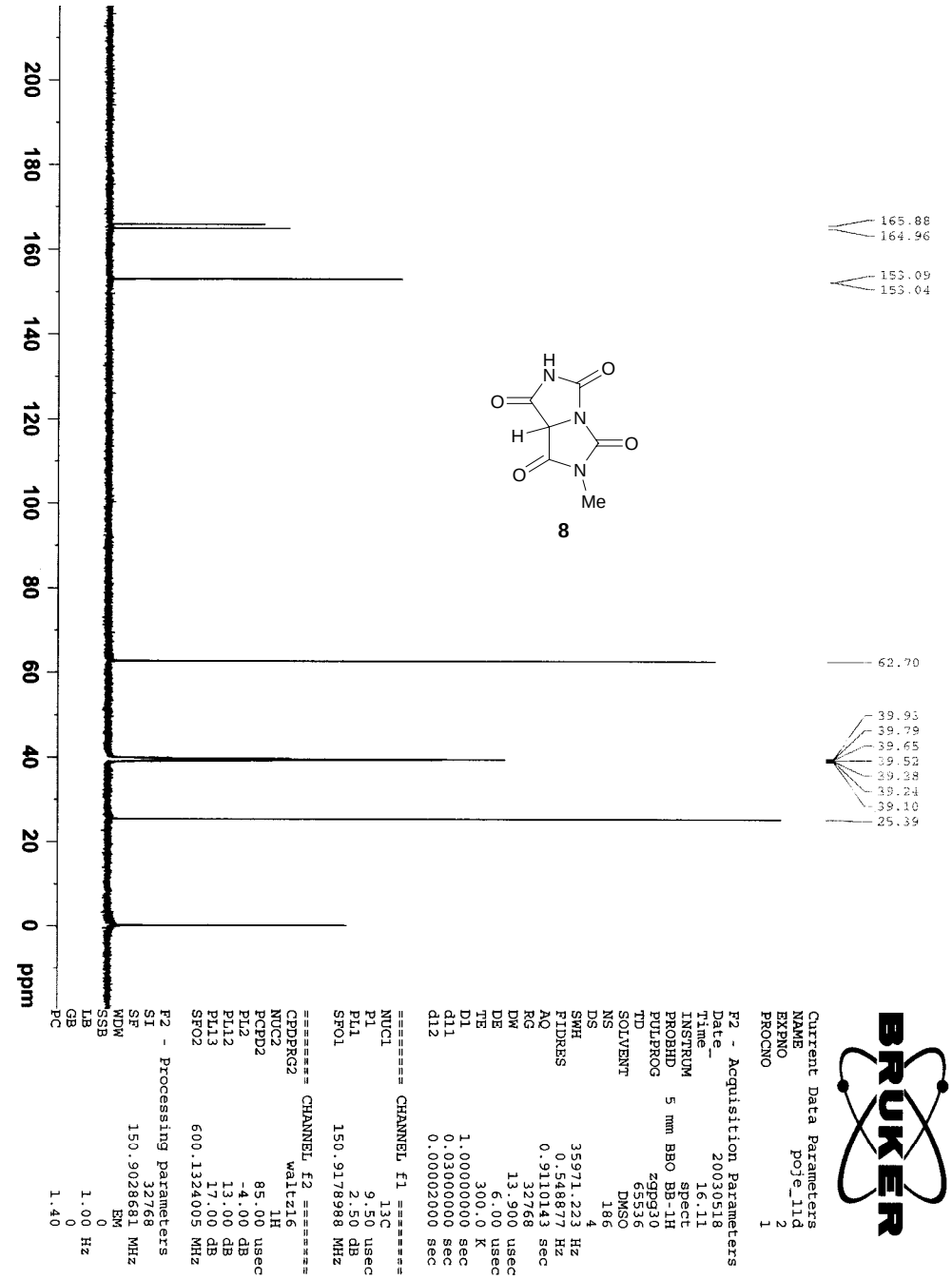


Figure S4b. ^{13}C NMR spectrum of **8** in DMSO-d_6

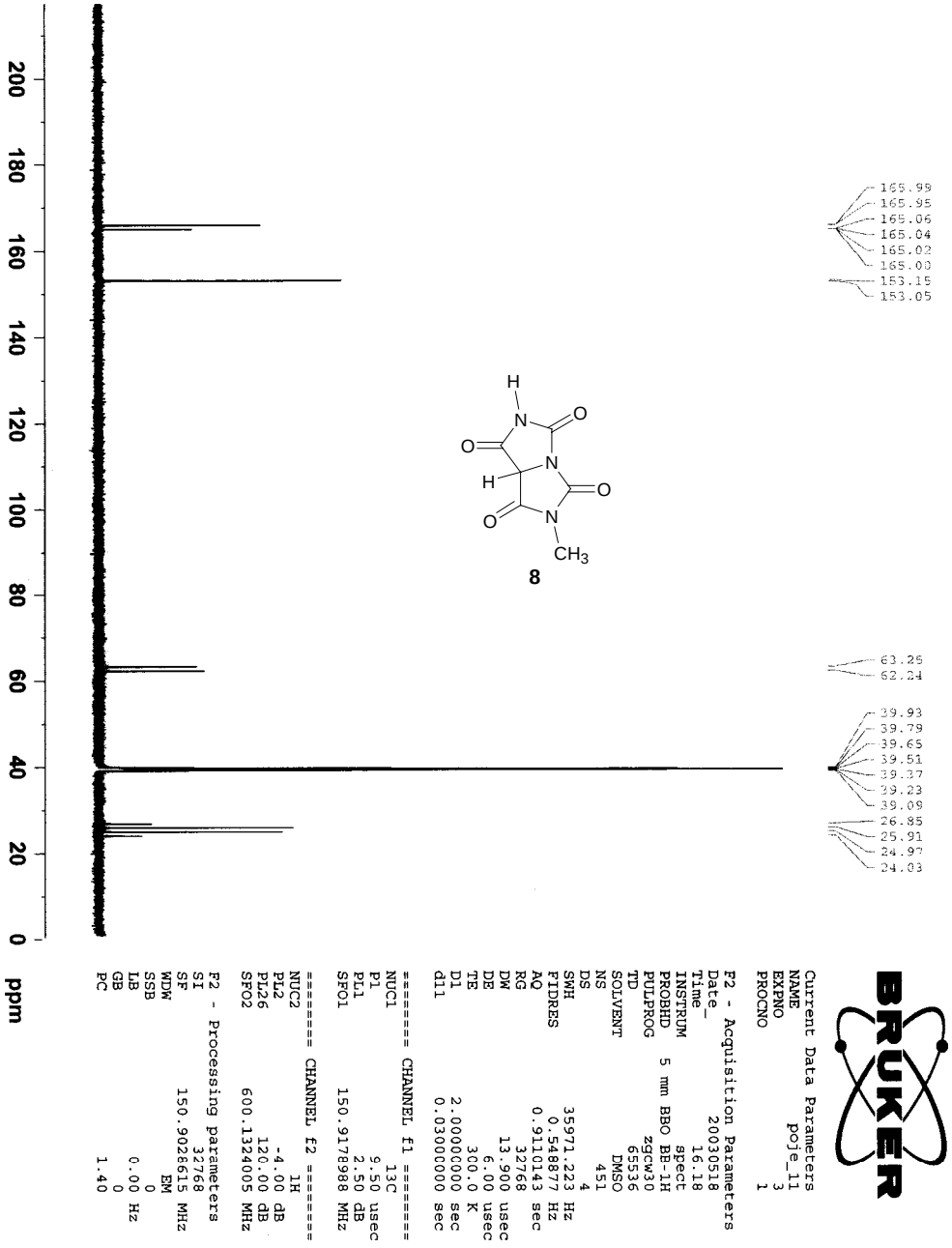


Figure S5. ^{1}H NMR spectrum of **8** in DMSO-d_6

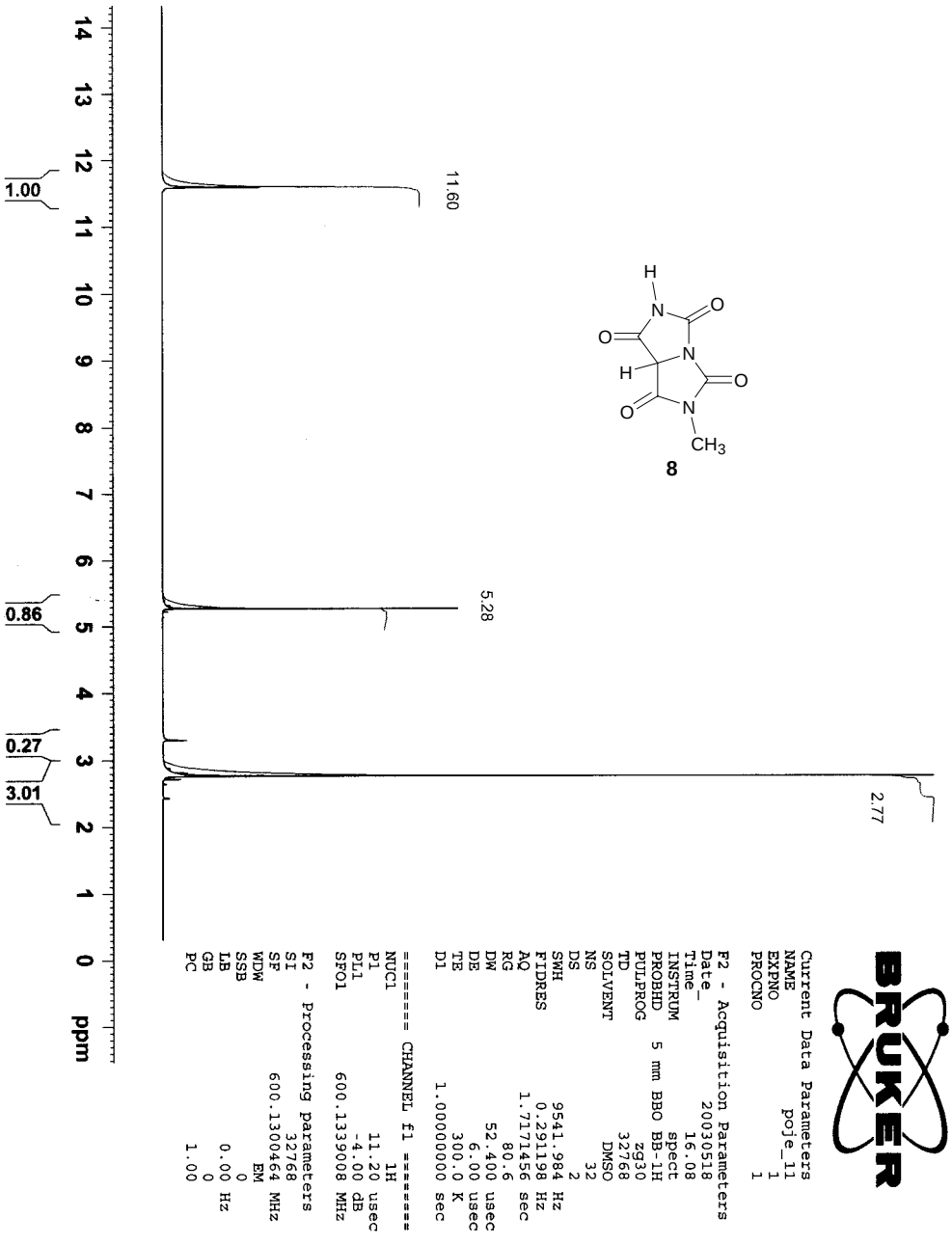


Figure S6. Mass spectrum of **8**