

Masateru Miyano* and Jeffrey N. Smith

Department of Medicinal Chemistry, G. D. Searle & Co., Box 5110, Chicago, Illinois 60680

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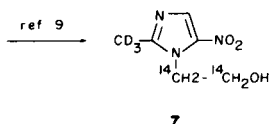
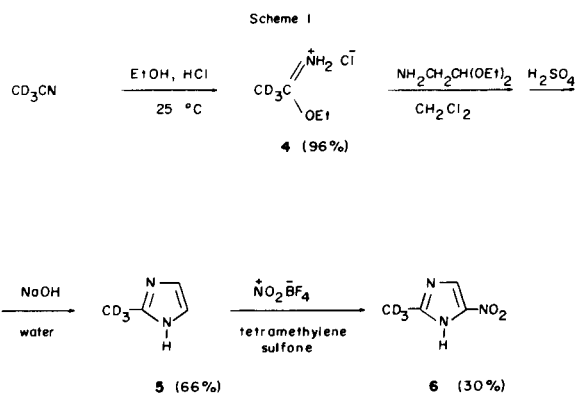
The title compound was prepared by two different procedures. The first route starts with acetonitrile- d_3 and goes through 2-trideuteriomethyl-5-nitroimidazole (**6**) (Scheme I). The second and more convenient process is direct labeling of metronidazole (**1**) with alkaline ethanol- d_1 .

J. Heterocyclic Chem., **19**, 659 (1982).

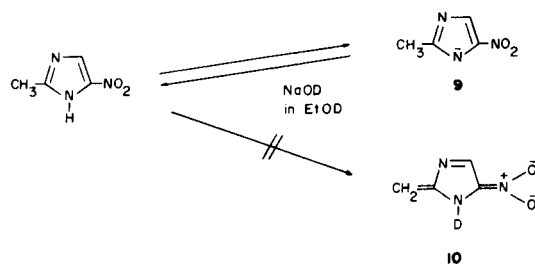
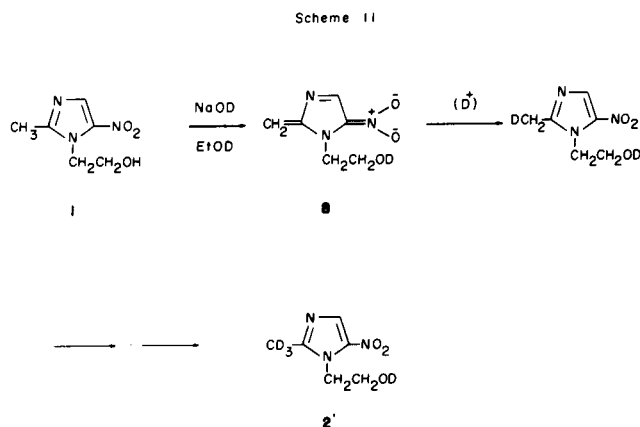
Metronidazole (**1**), 1-hydroxyethyl-2-methyl-5-nitroimidazole, exhibits broad antiprotozoal activity and has found widespread use in treating trichomoniasis (1,2). The metabolism of metronidazole in humans has been studied by several groups. In one study (3) the major metabolite isolated was 1-hydroxyethyl-2-hydroxymethyl-5-nitroimidazole (**3**). It is an interesting question whether or not the regiospecifically deuterated metronidazole (**2**) has an



extended biological half life due to the primary isotope effect. A synthesis of **2** is the subject of this communication.



Treatment of acetonitrile- d_3 (**5**) with equivalent amounts of dry hydrogen chloride in absolute ethanol afforded the crystalline iminoester hydrochloride (**4**) without loss of deuterium. The pmr spectrum of **4** in deuteriochloroform exhibited no methyl signal. Displacement of the ethoxy group in **4** with aminoacetaldehyde diethyl acetal followed



by cyclization in concentrated sulfuric acid gave rise to 2-methylimidazole- d_3 (**5**). The isotopic purity of **5**, as measured by pmr was 95 atom%; that is, 5% of the deuteriums were replaced with hydrogens. The pmr spectrum of regular 2-methylimidazole (**6**) in deuteriochloroform exhibited a peak at δ 2.40 (3H), whereas **5** indicated a very small multiplet at δ 2.40 (0.155H). The attempted nitration of **5** under classic conditions - for instance, hot fuming nitric acid - resulted either in no nitration or in major replacement of deuterium with hydrogen. However, nitronium fluoroborate could produce 2-methyl-5-nitroimidazole- d_3 (**6**) in 30% yield with little loss of deuterium. The pmr of regular 2-methyl-5-nitroimidazole (**7**) in pyridine- d_5 showed a peak at δ 2.38 (3H), while **6** exhibited a small multiplet of 0.166H. This gives 5.5% hydrogen or 94.5% deuterium in the 2-methyl group. A selective alkylation of N-1 of 2-methyl-5-nitroimidazole has been recorded in literature (8). Should a similar procedure be applied to **6** with a ^{14}C labeled alkylating agent (ethylene chloro-

Table

¹³C NMR of Metronidazole (1) and Metronidazole-d₃ (2) in Pyridine-d₅ (a)

Assignment			1		2	
	Multiplicity in off resonance	Intensity in decoupled spectrum	Chemical shift ppm from TMS	Intensity in decoupled spectrum	Chemical shift ppm from TMS	
=CH-	d	34	133.05	30	133.10	
-CH ₂ O-	t	63	60.76	48	60.73	
-CH ₂ -	t	62	49.03	56	49.01	
-CH ₃	q	20	14.55	-(b)	-(b)	

(a) Run on a Varian XL-100 spectrometer. (b) Could not be detected.

hydrin or ethylene oxide) metronidazole-¹⁴C-d₃ (7) would be prepared (9), which can be used for the subsequent metabolic studies.

Scheme II shows an alternate procedure for preparation of the regioselectively deuterated metronidazole (2) which is particularly convenient for a large scale preparation. Repeated treatments of commercially available (10) metronidazole with boiling ethanol-d₁ (5) containing sodium deuterioxide afforded 2' in which the C-2 methyl group was 99 atom % deuterated while no deuterium was detected on other carbons. An intermediate such as 8 may be envisaged as the solution of metronidazole in alkaline ethanol showed dark purple color which disappeared upon neutralization. It is interesting that the methyl group of 2-methyl-5-nitroimidazole was not deuterated at all under similar conditions. Apparently the aromatic anion 9 is preferred to the non-aromatic anion 10 in this case. Neither was 2-methylimidazole deuterated on alkaline ethanol treatment.

EXPERIMENTAL

Melting points were taken on a Thomas Hoover Unimelt and were uncorrected. ¹HMR spectra were run on a Varian T-60 spectrometer using TMS as an internal standard. Chemical shifts from TMS are reported as δ values in parts per million.

Ethyl Imidoacetate-d₃ Hydrochloride (4).

In a 50 ml flask was placed 10 g of acetonitrile-d₃ (5) and 10.45 g of absolute ethanol. This solution was cooled to an ice-salt bath, and 8.3 g of dry hydrogen chloride gas was passed in. The reaction mixture was then allowed to stand at 25° for 16 hours. At this point the flask was filled with a mass of clean crystals. They were broken up with the help of methylene chloride and then poured into anhydrous ether. The product was filtered under nitrogen and stored in a desiccator, 27.5 g (96%), mp 114-116° dec (11); pmr (deuteriochloroform): δ 4.70 (q, J = 7 Hz, 2H), 1.52 (t, J = 7 Hz, 3H), no signal for -CH₃.

2-Methylimidazole-d₃ (5).

In a 250 ml flask was placed 20 g of the imidate (4), 21.2 g of aminoacetaldehyde diethyl acetal, and 100 ml of dry methylene chloride. The reaction was slightly exothermic, so it was initially cooled in ice and then allowed to stand at 25° overnight. The solvent was removed and the residue was treated with 40 ml of concentrated sulfuric acid with cooling

to 0° for 3 hours. This solution was then added to 50% aqueous sodium hydroxide with cooling in ice. The solution was then saturated with sodium chloride and extracted repeatedly with chloroform. The organic portion was dried over sodium sulfate, treated with Darco, and concentrated to give 8.8 g (66%) of crystalline 5; pmr (deuteriochloroform): (6) δ 7.00 (s, 2H), 2.40 (m, 0.155H). This was accounted for 95% deuterium on the methyl group.

2-Methyl-5-nitroimidazole-d₃ (6).

In a 250 ml flask was placed 3.0 g of 95% deuterated 2-methylimidazole (5) and 40 ml of tetramethylene sulfone. This was then cooled in ice and treated with a solution of 8.23 g of nitronium tetrafluoroborate in 135 ml of tetramethylene sulfone. After 3 hours at 25° the reaction mixture was treated with ethyl acetate and water until the layers separated. The organic layer was then washed with saturated sodium chloride, dried over sodium sulfate, treated with Darco, and concentrated. The product was crystallized with benzene to give 0.52 g of 6 of mp 246-247°; pmr (pyridine-d₅): δ 8.23 (s, 1H), 2.38 (m, 0.166H). The δ 2.38 signal indicated 94.5% deuterium on the methyl group.

Metronidazole-d₃ (2).

In a 50 ml flask was placed 2.5 g of commercial metronidazole (10) and 25 ml of 95% ethanol-d₁ (5% deuterium oxide) (5). This was heated to reflux and 100 mg of clean sodium metal was added. It was then allowed to reflux for 0.5 hour and then returned to 25°. It stayed at 25° for 3 days. The product was filtered off as a colorless solid, 1.0 g. The mother liquor was acidified to pH 5 with 38% deuterium chloride in deuterium oxide (5) and concentrated. An additional 0.5 g of product crystallized from the mixture (total 1.5 g, 60%), mp 157-158 °C; pmr (pyridine-d₅): δ 8.04 (s, 1H), 4.48 (d, J = 5 Hz, 2H), 4.07 (d, J = 5 Hz, 2H), 2.55 (m, 0.334H). The δ 2.55 signal demonstrated 89% deuterium incorporation. In a 25 ml flask was placed 1.5 g of the 89% deuterated 2 and 10 ml of 95% ethanol-d₁. It was brought to reflux and treated with 100 mg of sodium metal. This solution was then allowed to reflux for 1 hour. It then stood at 25 °C overnight. The reaction mixture was cooled in ice, and the product was filtered to give 830 mg of 2, mp 156.5-158.5 °C; ¹pmr (pyridine-d₅): δ 8.18 (s, 1H), 4.50 (d, J = 5 Hz, 2H), 4.06 (d, J = 5 Hz, 2H), no methyl signal. The uv (methanol) of 2, λ max 308 nm (ε 7,420) was in good agreement with the uv (methanol) of regular metronidazole (1); λ max 309 nm (ε 7,000).

Anal. Calcd. for C₆H₅D₃NO₂: C, 41.40; H, 5.26; N, 24.10. Found: C, 41.34; H, 5.29; N, 24.24.

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- (3) J. E. Stambaugh, L. G. Feo and R. W. Manthei, *Life Sci.*, **6**, 1811 (1967).
- (4) A number of deuterium isotope effects in biologic reactions have been known. For review see M. I. Blake, H. L. Crespi and J. J. Katz, *J. Pharm. Sci.*, **64**, 367 (1975).
- (5) Purchased from Merck Chemical Division, Merck & Co., Inc., minimum isotopic purity of 99 atom%.
- (6) The pmr of **5** was compared with 2-methylimidazole (99%, mp 142-143°) purchased from Aldrich Chemical Co., Inc.
- (7) The pmr and mp of **6** were compared with 2-methyl-5-nitroimidazole 99%, mp 252-254°) purchased from Aldrich Chemical Co., Inc.
- (8) C. Cosar, C. Crissan, R. Horeclois, R. M. Jacob, J. Robert, S. Tchelitcheff, and R. Vaurpé, *Arzneim.-Forsch.*, **16**, 23 (1966).
- (9) This was indeed carried out by Dr. K. F. King and colleague of G. D. Searle & Co.
- (10) The trade name is Flagyl.
- (11) A. Pinner, *Ber.*, **16**, 1643 (1883), mp 98-100°.