

SYNTHESIS OF DEUTERIUM-LABELED 7-AZANORBRNANE AND 2-AZABICYCLO[2.2.2]-
OCTANE DERIVATIVES

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SUMMARY

The syntheses of four specifically-deuterated 2,3-benzo-7-azanorbornane derivatives and three specifically-deuterated 5,6-benzo-2-azabicyclo[2.2.2]octane derivatives are described.

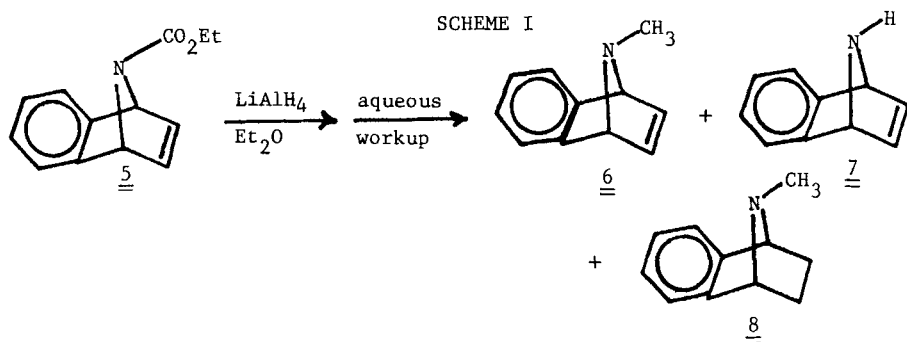
Key Words: Synthesis, deuterium-labeled, 7-azanorbornanes, 2-azabicyclo[2.2.2]-octanes

INTRODUCTION

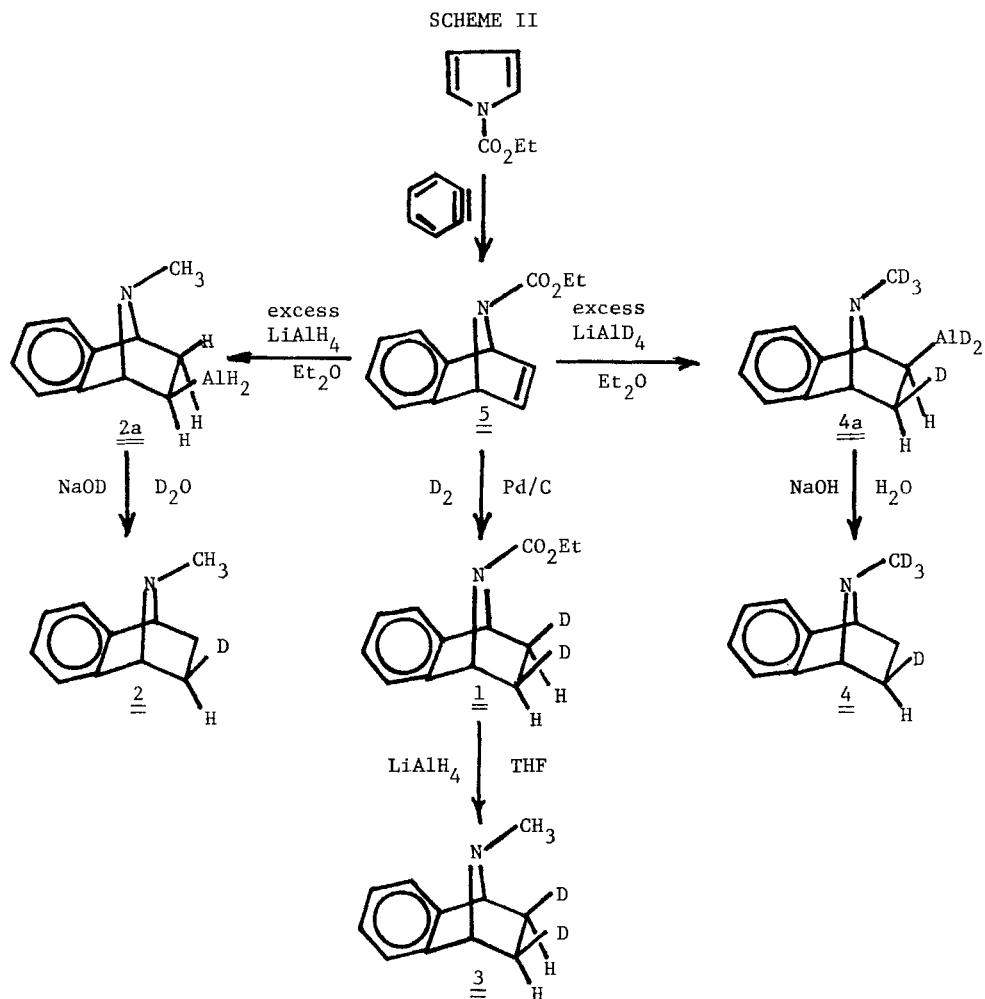
As part of continuing investigations into the chemistry of azabicyclic systems¹⁻⁴, we have recently undertaken a detailed study of the mass spectra of some 7-azanorbornane and 2-azabicyclo[2.2.2]octane derivatives.⁵ In an effort to elucidate the mechanistic pathways by which compounds of this type fragment under electron impact, we have synthesized a number of specifically-deuterated 7-azanorbornane and 2-azabicyclo[2.2.2]octane derivatives. We report herein the synthesis of four specifically-deuterated 2,3-benzo-7-azanorbornanes (1 - 4) and three specifically-deuterated 5,6-benzo-2-azabicyclo[2.2.2]octane derivatives (9 - 11). The methods employed to effect the syntheses of these compounds are outlined below.

DISCUSSION

In a previous communication¹, we reported that lithium aluminum hydride reduction of N-carbethoxy-7-aza-2,3-benzonorbornadiene (5) followed by workup with aqueous sodium hydroxide solution afforded a mixture of three products (6, 7, and 8: see Scheme I and Experimental Section). Compounds 6, 7, and 8 could be conveniently separated via preparative vapor phase chromatography (VPC). Compound 8 and its specifically-deuterated analogs 2, 3, and 4 were synthesized using various combinations of LiAlH₄ (or LiAlD₄) reduction of 5⁴ followed by aqueous workup with NaOH-H₂O (or NaOD-D₂O: see Scheme II). Structures 2a and 4a (Scheme II) have been suggested as inter-

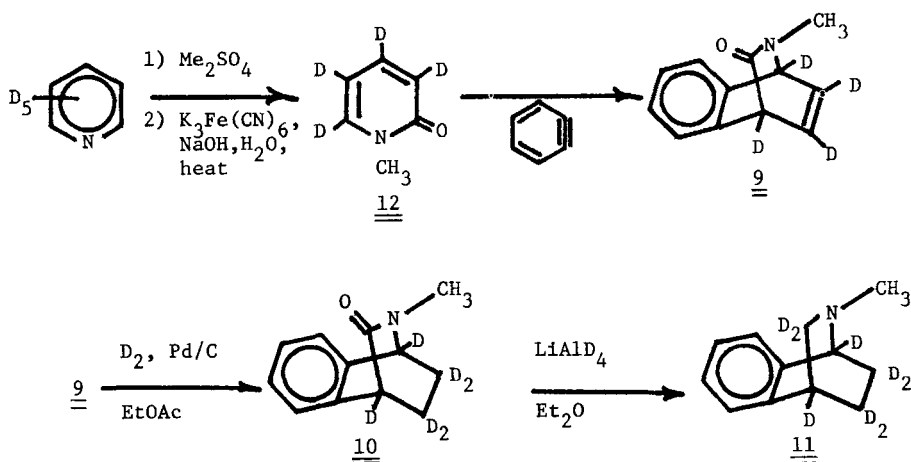


mediates when compounds 2 and 4, respectively, are synthesized by this method.¹ Intermediates 2a and 4a are believed to be the initial products which are formed when compound 5 is reduced with LiAlH_4 and with LiAlD_4 , respectively.¹



Sheinen, *et al.*⁶ have reported synthesizing unlabeled 9 via Diels-Alder addition of benzyne (generated *in situ* from anthranilic acid and isoamyl nitrite) to N-methyl-2-pyridone.⁷ In our hands, this procedure invariably afforded 9 contaminated with isoamyl alcohol. To circumvent this difficulty, benzenediazonium-2-carboxylate was prepared separately,⁸ and the resulting dry diazonium salt was decomposed thermally in the presence of an equimolar amount of N-methyl-2-pyridone-3,4,5,6- d_4 (12). Catalytic deuteration of 9 afforded 10 which could be further reduced with lithium aluminum hydride to afford 11, (Scheme III).

SCHEME III



EXPERIMENTAL METHODS

Melting points were obtained on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Elemental microanalyses were performed on unlabeled compounds by Chemalytics, Inc., Tempe, Arizona. Analytical and preparative vapor phase chromatography (VPC) were performed on a Varian 90-P gas chromatograph. Product identification was aided by analysis of electron impact mass spectra which were obtained utilizing a Hitachi Perkin-Elmer Model RMU-6E mass spectrometer. Details of the mass spectrometry study will be published elsewhere.⁵ NMR spectra were obtained on a Varian T-60 NMR spectrometer. Infrared spectra were obtained on a Beckman Instruments Model IR-7 recording infrared spectrophotometer.

N-Carboethoxy-7-aza-2,3-benzonorbornene-exo-5,exo-6- d_2 (1).—Compound 1 was synthesized by a published procedure⁴ in 96% yield via reduction of N-carboethoxy-7-aza-2,3-benzonorbornadiene (5) using deuterium gas (45 psig) over 5% palladium on charcoal catalyst. The assignment of *exo,exo* stereochemistry to the 5,6-carbon-deuterium bonds in 1 was accomplished via compari-

son of its 60 MHz NMR spectrum with the corresponding published⁴ spectrum of unlabeled 1.

N-Methyl-7-aza-2,3-benzonorbornene-exo-5,exo-6-d₂ (3).— A solution of 1 (5.0 g, 23 mmol) in dry tetrahydrofuran (20 ml) was added dropwise to a stirred solution of lithium aluminum hydride (0.91 g, 24 mmol) in dry tetrahydrofuran (30 ml). After refluxing for 8 h, the cooled reaction mixture was quenched by successive addition of water (1 ml), 10% aqueous sodium hydroxide solution (1 ml), and water (3 ml). The resulting mixture was then filtered to remove precipitated aluminum salts, and the filtrate was dried (Na₂SO₄). The resulting mixture was then filtered, and the filtrate was concentrated to afford crude 3. Sublimation of the crude product (50°C, 0.1 mm Hg) afforded pure 3 (3.04 g, 83%) as a colorless, waxy solid. Proton NMR spectrum (CDCl₃ solvent): δ 1.17 (singlet, 2H, endo-5,endo-6 protons); δ 2.04 (singlet, 3H, N-CH₃); δ 4.05 (singlet, 2H, 1,4- protons); δ 7.15 (broad singlet, 4H, aromatic ring protons).

Reduction of N-Carboethoxy-7-aza-2,3-benzonorbornadiene (5) with Lithium Aluminum Hydride.— The general procedure utilized for these reductions is as follows: A solution of 5⁴ (4.65 mmol) in dry ether (10 ml) was added dropwise to a refluxing solution of lithium aluminum hydride (4.0 mmol) in dry ether (15 ml). After refluxing for 8 h, the cooled reaction mixture was quenched by successive addition of water (4 drops), 10% aqueous sodium hydroxide solution (4 drops), and water (10 drops). The resulting mixture was then filtered to remove precipitated aluminum salts, and the filtrate was dried (Na₂SO₄). The dry ethereal solution was then filtered, and the filtrate was concentrated. The resulting oil, which was found to contain a mixture of 6, 7, and 8,¹ was separated via preparative VPC techniques utilizing a 0.64 cm x 3 m 25% FFAP on Chromasorb W column, (column temperature 150°C, He flow rate 120 ml/min). The relative yields (retention times, min) of products 6, 7, and 8 were found to be 61%(8.6), 6%(14.8), and 33%(4.6), respectively. Proton NMR spectrum of 6 (CDCl₃ solvent): δ 2.1 (broad singlet, 3H, N-CH₃); δ 4.5 (broad singlet, 2H, 1,4- protons); δ 6.7-7.3 (complex multiplet, 6H, aromatic ring and vinyl protons). Proton NMR spectrum of 7 (CDCl₃ solution): δ 3.0 (singlet, 1H, N-H); δ 4.9 ("unsymmetrical triplet", 2H, 1,4- protons); δ 6.7-7.3 (complex multiplet, 6H, aromatic ring and vinyl protons). Proton NMR spectrum of 8 (CDCl₃ solvent): δ 1.13 (doubled doublet, J_{5n5x} = 11 - 12 Hz, J_{5n6x} = 3 - 4 Hz, 2H, endo-5,endo-6 protons); δ 2.04 (singlet, 3H, N-CH₃); δ 2.12 (multiplet, 2H, exo-5,exo-6 protons); δ 4.02 (multiplet, 2H, 1,4- protons); δ 7.12 (broad singlet, 4H, aromatic ring protons). IR spectrum of 8 (film, NaCl disc): 3060(m), 2980(m), 1260(sh,m), and 760 cm⁻¹ (s).

N-Methyl-2-pyridone-3,4,5,6-d₄ (12).⁷ Dimethyl sulfate (37.8 g, 0.3 mol) was added dropwise to pyridine-d₅ (25 g, 0.3 mol) over a 15 min period. The resulting mixture was heated on a steam bath for 2 h and then diluted with water (50 ml). A solution of K₃Fe(CN)₆ (196 g, 0.6 mol) in water (390 ml) and a solution of sodium hydroxide (49.0 g, 1.23 mol) in water (50 ml) were then added to the reaction mixture. Dropwise addition of these two aqueous solutions was conducted using separate addition funnels such that the aqueous sodium hydroxide solution was completely added by the time that one-half of the aqueous K₃Fe(CN)₆ solution had been added. The temperature of the reaction mixture was maintained below 10°C via periodic application of an ice-salt bath. The reaction mixture was stirred for 2 h after the addition of reactants had been completed. The reaction mixture was then saturated with sodium carbonate, and the resulting mixture was filtered. The filtrate was extracted with chloroform; the organic layer was dried (anhydrous Na₂SO₄), filtered, and then concentrated (rotary evaporator). The residual oil was distilled under reduced pressure; the fraction having bp 116–118°C (9 mm Hg) was collected. The yield of colorless oil was 24.5 g (73%), which was found by VPC analysis to be greater than 98% pure. The 60 MHz NMR spectrum of the product (neat liquid) displayed only a single sharp resonance at δ 3.56 (N-CH₃).

N-Methyl-2-aza-3-keto-5,6-benzobicyclo[2.2.2]octa-5,7-diene-1,4,7,8-d₄ (9).—Compound 12 (5.0 g, 0.052 mol) and dry benzenediazonium-2-carboxylate [synthesized⁸ from anthranilic acid (6.85 g, 0.050 mol)] were combined in dichloromethane (100 ml); the resulting mixture was refluxed for 2.5 h. The resulting clear, dark solution was washed successively with 5% aqueous potassium hydroxide solution (1 x 100 ml) and with water (3 x 100 ml). The organic layer was dried (Na₂SO₄), filtered, and then concentrated on a rotary evaporator. The resulting viscous, black oil was further purified via elution chromatography on neutral alumina (3:1 hexane-ethyl acetate eluent). A colorless oil was thereby obtained which, after trituration with hexane, afforded solid 9 (1.1 g, 11%). Sublimation (100°, 0.1 mm Hg) afforded pure 9, mp 97–98°C (lit.⁶ mp 98–100°C).

N-Methyl-2-aza-3-keto-5,6-benzobicyclo[2.2.2]oct-5-ene-1,4,7,7,8,8-d₆ (10).—Compound 9 (1.0 g, 5.4 mmol) was dissolved in ethyl acetate (25 ml) and reduced with deuterium gas (45 psig) over 5% palladium on charcoal catalyst on a Parr apparatus for 30 min. The reaction mixture was then filtered to remove catalyst, and the solution was concentrated to a volume of 5 ml. Trituration with hexane afforded 10 (0.93 g, 92%). Recrystallization from hexane afforded colorless needles, mp 130–131°C (lit.⁹ mp 133–135°C, corrected).

N-Methyl-2-aza-5,6-benzobicyclo[2.2.2]oct-5-ene-1,3,3,4,7,7,8,8-d₈

(11).- Reduction of 10 with excess lithium aluminum deuteride in ether according to a previously published procedure⁴ afforded 11. The 60 MHz proton NMR spectrum of 11 thereby obtained consisted of only two singlets: a broad singlet at δ 7.1 (area 4H, aromatic protons) and a sharp singlet at δ 2.0 (area 3H, N-CH₃), (CDCl₃ solvent).

ACKNOWLEDGMENT

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