ethereal solution was washed (2% aqueous $NaHCO_3$, H_2O, saturated aqueous NaCl), dried ($MgSO_4$), and concentrated. The crude product was recrystallized from ligroin to provide 194 mg (1.06 mmol, 85%) of 7-hydroxycadalene, mp 116–120 °C. The spectral data of this material were in agreement with those previously published for this compound.[26]

Acknowledgment. We thank Jan Donovan for excellent technical assistance and Cotton Inc. for generous financial support of the work carried out at the University of Missouri.

Registry No. (±)-**1**, 87900-51-4; (±)-**2**, 56051-00-4; **3**, 77401-25-3; **4**, 68233-94-3; **4** 3,5-dinitrobenzoate, 68233-95-4; **5** (R = Et), 87843-16-1; (±)-**6**, 70143-23-6; **8** (isomer 1), 87843-17-2; **8** (isomer 2), 87843-18-3; (±)-**9**, 70143-24-7; (±)-**10**, 80736-45-4; (±)-**11**, 70143-25-8; (±)-**12** (isomer 1), 87843-19-4; (±)-**12** (isomer 2), 87843-20-7; **13**, 77996-13-5; **15**, 68233-93-2; (±)-**16**, 87843-21-8; (±)-**17** (isomer 1), 87843-22-9; **17** (isomer 2), 87843-23-0; **18**, 87843-24-1; **19**, 2102-75-2; isopropyl bromide, 75-26-3.

Applications of Intramolecular Amidomercuration. 2.[1] Synthesis of *trans*-5-Hydroxy-2-propylpiperidine, (±)-Pseudoconhydrine

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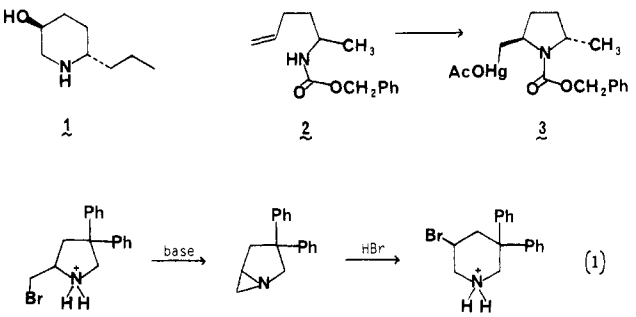
A method for the stereoselective conversion of δ-alkenyl carbamates into *trans*-2-alkyl-5-substituted-piperidines utilizing intramolecular amidomercuration as a key step has been developed. As a specific illustration of the method, a synthesis of one of the Hemlock alkaloids, (±)-pseudoconhydrine (*trans*-5-hydroxy-2-propylpiperidine, **1**) was completed. The organomercurial **7a** obtained from the intramolecular amidomercuration of 4-[(carbobenzyloxy)amino]-7-octene (**6**) was converted to the corresponding *trans*-5-(iodomethyl)-2-propylpyrrolidine derivative **7b**. Cleavage of the carbamate and treatment with base generated the bicyclic aziridine 2-*exo*-propyl-1-azabicyclo[3.1.0]hexane (**8a**). Treatment of this aziridine with excess trifluoroacetic acid gave ring opening to the disubstituted pyrrolidine derivative **9a** exclusively. Ring opening of the analogous aziridine **8b** with HCl gave mixtures of pyrrolidine **9b** and piperidine **10b**. However, these derivatives can be equilibrated through the neutral amine to a mixture consisting of ca. 85% of the piperidine derivative. Slow addition of trifluoroacetic acid to aziridine **8a** allowed for equilibration to piperidine **14** as the major product. Hydrolysis and purification gave pure racemic pseudoconhydrine. This synthetic sequence illustrates a synthetic equivalent to anti-Markovnikov cyclofunctionalization of δ-alkenyl carbamates. In addition, this study provided new information on the regiochemistry of ring opening of bicyclic aziridines.

As part of our investigation of the synthetic utility of intramolecular amidomercuration reactions,[1] we have examined the conversion of δ-alkenyl carbamates into *trans*-2-alkyl-5-substituted-piperidines. As a specific illustration of the utility of this method, we have completed a stereoselective synthesis of racemic pseudoconhydrine (**1**), one of the Hemlock alkaloids.[2] The synthesis is based on our previous demonstration that mercuric ion initiated cyclization of δ-alkenyl carbamates leads to formation of *trans*-pyrrolidine derivatives with high stereoselectivity (**2** → **3**)[1] and the reported[3] conversion of halomethylpyrrolidines into 3-substituted piperidines through bicyclic aziridine intermediates (e.g., eq 1). These studies have led also to important new observations regarding the regiochemistry of the ring opening of such bicyclic aziridines.



The carbamate **6** used for the synthesis of **1** was prepared in straightforward fashion. The known ketone **5**[2b] was prepared by oxidation of alcohol **4** obtained by addition of the Grignard reagent from 4-bromobutene to butyraldehyde. In analogy with our earlier preparation of **2**,[1] ketone **5** was converted to its oxime, reduced, and acylated with benzyl chloroformate to give **6** in 91% yield. The cyclization of this carbamate was effected by treatment with mercuric acetate in tetrahydrofuran. The resulting organomercury intermediate **7a** was treated with KI and then I_2[4] to give the iodo compound **7b** in 78% yield. This iodo compound could also be prepared by iodine-in-

(1) For paper 1 in this series, see: Harding, K. E.; Burks, S. R. *J. Org. Chem.* **1981**, *46*, 3920–3922. We have applied the term amidomercuration to cyclizations involving both amide and carbamate functional groups. Cyclizations involving carbamates have been termed ureidomercuration by others (Danishefsky, S.; Taniyama, E.; Webb, R. R., II *Tetrahedron Lett.* **1983**, *24*, 11–14) even though rules of nomenclature indicate that "ureido" is a prefix for a NH_2CONH group: Rule C-971.2, IUPAC Rules for Nomenclature of Organic Compounds. See Riguady, J.; Klesney, S. P. "Nomenclature of Organic Chemistry", Sections A–F and H; Pergamon Press: New York, 1979; p 297.

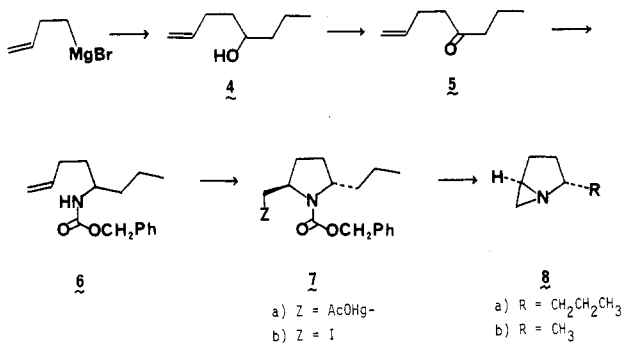
(2) (a) Gross, D. *Fortschr. Chem. Org. Naturst.* **1971**, *29*, 1–59. (b) Brown, E.; Lavoue, J.; Dahl, R. *Tetrahedron* **1973**, *29*, 455–461 and references cited therein. (c) Marion, L.; Cockburn, W. F. *J. Am. Chem. Soc.* **1949**, *71*, 3402–3404. (d) Gruber, W.; Scholgl, K. *Monatsh. Chem.* **1949**, *80*, 499–505. (e) Sorm, F.; Sicher, J. *Collect. Czech. Chem. Commun.* **1949**, *14*, 331–344.

(3) (a) Horning, D. E.; Muchowski, J. M. *Can. J. Chem.* **1974**, *52*, 1321–1330. (b) Logothetis, A. L. *J. Am. Chem. Soc.* **1965**, *87*, 749–754.

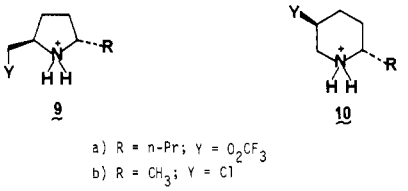
(4) (a) Jensen, F. R.; Rickborn, B. "Electrophilic Substitution of Organomercurials"; McGraw-Hill: New York, 1968. (b) Larock, R. C. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 27–37. (c) Paquette, L. A.; Storm, P. C. *J. Org. Chem.* **1970**, *35*, 3390–3393. (d) Larock, R. C. *Ibid.* **1974**, *39*, 834–836. (e) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 7612–7613.

0022-3263/84/1949-0040$01.50/0

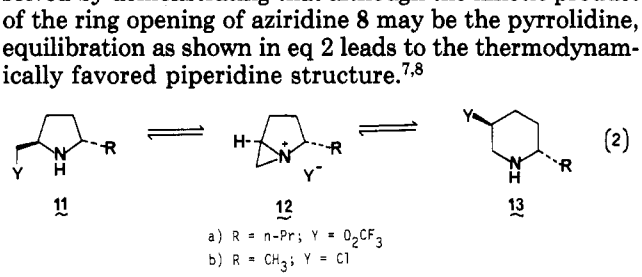
itiated cyclization[5] with iodonium di-*sym*-collidine perchlorate,[6] but this procedure is disadvantageous since it required use of 1 equiv of expensive silver perchlorate.[6] The carbamate group was removed by treatment with hydrogen bromide in acetic acid. The resulting hydrobromide (84% yield) was suspended in water and treated with sodium carbonate to effect ring closure to the aziridine **8a**.



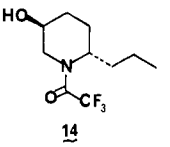
Although bicyclic aziridines related to **8** have been reported to ring open specifically to piperidine products upon treatment with electrophilic reagents,[3] we found that treatment of aziridine **8a** or **8b** with an excess of a protic acid and isolation as the ammonium salt gave the corresponding pyrrolidine **9** as the major product under many of the reaction conditions we investigated. Thus, treatment of aziridine **8a** with 2 or more equiv of trifluoroacetic acid in D_2O at room temperature or CH_2Cl_2 at −78 °C gave only the pyrrolidine derivative **9a**. Reaction in $CDCl_3$ at room temperature or in hexane at −78 °C gave mixtures containing less than 20% piperidine **10a**. Analogously,



treatment of **8b** (prepared from **3** by the method used for conversion of **7a** → **8a**) with gaseous HCl in $CDCl_3$ gave a product consisting predominantly of the pyrrolidine hydrochloride **9b** and piperidine **10b** in a ratio of approximately 68:32. However, reaction in hexane or toluene gave about a 30:70 ratio of **10a** and **10b**. The product ratios were determined by analysis of the NMR spectra. These results, which seriously jeopardized the initial synthetic plan, demonstrate that the regiochemistry of ring opening of bicyclic aziridines is more complex than suggested by earlier reports[3] on these reactions. This problem was solved by demonstrating that although the kinetic product of the ring opening of aziridine **8** may be the pyrrolidine, equilibration as shown in eq 2 leads to the thermodynamically favored piperidine structure.[7,8]



Thus, conversion of a mixture of pyrrolidine hydrochloride **9b** and the corresponding piperidine hydrochloride **10b** into the free amines **11b** and **13b** resulted in equilibration through aziridinium ion **12b** to give material consisting of approximately 85% piperidine **13b** upon isolation as the hydrochloride salt. This result indicates that the pyrrolidine product is the kinetic product of aziridine opening, but that under conditions allowing equilibration, the piperidine predominates as the thermodynamically favored product.[8] This observation provided the information necessary to develop a method for converting the aziridine **8a** into **1**. Slow addition of 1 equiv of trifluoroacetic acid to **8a** in an organic solvent followed by a period of 12–16 h at room temperature gave material that, by NMR analysis, contains ca. 85% of the piperidine **14**.[9,10] Hydrolysis of the trifluoroacetyl group of **14** with



potassium carbonate in methanol and purification by distillation and sublimation gave pure racemic pseudoconhydrine (**1**).[11] This synthesis thus demonstrates methodology for the stereoselective conversion of δ-alkenyl carbamates into 5-substituted piperidine derivatives (**6** → **13**), a conversion equivalent to anti-Markovnikov cyclofunctionalization of these derivatives.

Experimental Section

General Procedures. Infrared spectra were recorded on a Pye Unicam Model SP3 infrared spectrophotometer. The ^1H NMR spectra were obtained on a Varian Associates Model EM-390 or XL-200 spectrometer. The ^{13}C NMR spectra were obtained on a JEOL PFT-100 spectrometer system operating at 25.034 MHz (proton resonance frequency 99.539 MHz) and equipped with a Nicolet 1085 data system or on a Varian Associates Model FT-80

(5) For examples of iodine-initiated cyclofunctionalization of amides, see: (a) Aida, T.; Legault, R.; Dugat, D.; Durst, T. *Tetrahedron Lett.* **1979**, 4993–4994. (b) Biloske, A. J.; Wood, R. D.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 3233–3235.

(6) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190–2198.

(7) This equilibration was first encountered in our studies in a case where treatment of **9** (R = CH_3, Y = I) in $CDCl_3$ with aqueous sodium carbonate (or in THF with NaH) followed by reaction with gaseous HCl led to isolation of the hydrochloride of 5-iodo-2-methylpiperidine (**13**, Y = I, R = CH_3): mp 160–162 °C; ^1H NMR (200 MHz, D_2O) δ 1.05 (d, J = 6.5 Hz, 3 H, CH_3), 1.2–1.5 (m, 1 H), 1.5–2.1 (m, 2 H), 2.2–2.4 (m, 1 H), 3.0–3.3 (m, 1 H), 3.2 (t, J = ca. 12.5 Hz, 1 H, C-6 H_a), 3.6 (ddd, J = 1.85, 4.3, and 12.5 Hz, 1 H, C-6 H_e), 4.0 (tt, J = 4.3 and 12.2 Hz, 1 H, C-5 H); ^{13}C NMR (25.034 MHz, $CDCl_3$) δ 14.6 (C-5), 18.7 (CH_3), 32.3 and 35.3 (C-2 and C-4), 51.9 (C-6), 52.2 (C-2). This result requires that the base treatment under these conditions did not lead to aziridine formation but only to the neutral amine **11**, which equilibrated to piperidine **13**.

(8) For examples of equilibration of *N*-alkyl-2-(halomethyl)pyrrolidine and *N*-alkyl-3-halopiperidine derivatives, see: (a) Hammer, C. F.; Heller, S. R.; Craig, J. H. *Tetrahedron* **1972**, *28*, 239–253. (b) Surzur, J.-M.; Stella, L.; Tordo, P. *Bull. Soc. Chim. Fr.* **1970**, 115–127. (c) Reference 3a. Evidence for the stereochemical integrity during the equilibration represented by eq 2 is presented in ref 7a.

(9) Derivatives of *N*-alkyl-2-(hydroxymethyl)pyrrolidines and *N*-alkyl-3-hydroxypiperidines have been equilibrated: Paul, R.; Tchelitcheff, S. *Bull. Soc. Chim. Fr.* **1958**, 736–741. The equilibrium for the acetate derivatives is reported to be ca. 80:20, favoring the piperidine structure.

(10) Without an excess of acid present to trap the amines **11a** and **13a** as the protonated salts, the trifluoroacetate group apparently is transferred slowly from oxygen to nitrogen (e.g., **13a** → **14**). For examples of reaction of alkyl trifluoroacetates with amines, see: Curphey, T. J. *J. Org. Chem.* **1979**, *44*, 2805–2807. Curphey, T. J.; Daniel, D. S. *Ibid.* **1978**, *43*, 4666–4668. Bayer, E.; Hunziker, P.; Mutter, M.; Sievers, R. E.; Uhmann, R. *J. Am. Chem. Soc.* **1972**, *94*, 265–268. Slusarczuk, G. M. J.; Joullie, M. M. *Chem. Commun.* **1970**, 469. Saroff, H. A.; Karmen, A. *Anal. Biochem.* **1960**, *1*, 344–350. Weygand, F.; Geiger, R. *Chem. Ber.* **1959**, *92*, 2099–2106.

(11) The overall yield for the conversion of ketone **6** into pure, crystalline (±)-pseudoconhydrine is 30%. The first published syntheses of racemic pseudoconhydrine[2c–e] utilized a low-yield (ca. 30%) reduction of 5-hydroxy-2-propylpyridine as the last step in the reaction. The synthesis by Brown et al.[2b] gave (±)-pseudoconhydrine hydrochloride in 24% yield from 8-methyl-7-nonen-4-one.

(20.00 MHz) or Model XL-200 (50.31 MHz) spectrometer. All chemical shifts are reported on the δ scale as parts per million downfield from tetramethylsilane. The spectra obtained in D_2O utilized CH_3CN as internal standard: $\delta(CH_3CN) = 1.93$ ppm (^1H NMR) and 1.3 ppm (^{13}C NMR).

Melting points were taken with a Thomas-Hoover capillary melting point apparatus. All melting and boiling points are uncorrected. Preparative-layer chromatography was performed with Brinkman silica gel 60 GF254. "Brine" refers to a saturated aqueous solution of sodium chloride. After the solution was dried with the stated drying agent (normally a 1:1 mixture of $MgSO_4$ and Na_2SO_4) and filtered, the solvent was removed ("concentrated") at ca. 30 mm with a rotary evaporator. Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. The temperatures cited for these distillations are the maximum temperature of the oven during the distillation.

7-Octen-4-ol (4). A solution of 4-bromobutene (1.0 mL, 9.8 mmol) in ca. 2 mL of dry ether was added dropwise at room temperature under nitrogen to a stirred mixture of 0.5 g (20.57 mmol) of magnesium turnings (activated by the addition of a small amount of iodine) and ca. 15 mL of dry ether. Dropwise addition was regulated to maintain a gentle reflux. After the alkyl bromide addition was complete, the mixture was stirred an additional 30 min at room temperature and then was chilled to 0 °C in a brine/ice bath. To this chilled solution was added 0.5 mL (5.66 mol) of butyraldehyde in 2 mL of dry ether. The ice bath was removed, and the mixture was allowed to warm to room temperature, heated to reflux for 1 min, cooled to room temperature, and quenched with the addition of ammonium chloride solution. The resulting mixture was washed (water, bicarbonate, and brine), dried over $MgSO_4$, filtered, and concentrated. The crude alcohol was chromatographed on silica gel with hexane/ethyl acetate (9:1) and evaporatively distilled (7 mm, 80 °C) to yield 483 mg (66% yield) of pure alcohol **4**: IR (film) 3340 (OH), 1644 ($HC{=}CH_2$), 915 ($CH{=}CH_2$) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.95 (t, 3 H, CH_3), 1.2–1.7 (m, 6 H, CH_2), 1.9 (br s, 1 H, OH), 2.0–2.5 (m, 2 H, allylic CH_2), 3.4–3.8 (m, 1 H, HCOH), 4.8–5.2 (m, 2 H, $CH_2{=}CH$), 5.6–6.1 (m, 1 H, $CH{=}CH_2$); ^{13}C NMR (25.034 MHz, $CDCl_3$) δ 14.1 (C-1), 18.9 (C-2), 30.1 (C-3), 36.7 and 39.8 (C-5 and C-6), 71.1 (C-4), 114.5 (C-8), 138.7 (C-7).

7-Octen-4-one (5). To a flask containing a stirred suspension of 250 mL of dry CH_2Cl_2, 35 g (0.16 mol) of pyridinium chlorochromate, and 80 g of Celite was added 10.5 g (0.082 mol) of alcohol **4** in 20 mL of dry CH_2Cl_2.[12] The mixture was stirred for 2.5 h, diluted with 500 mL of dry ether, and filtered through Florisil. Concentration and microdistillation (0.1 mm, 90 °C) yielded 7.1 g (68% yield) of known ketone **5**:[2b] IR (film) 1705 (C=O), 915 and 1000 (C=C) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.9 (t, J = 7.5 Hz, 3 H, CH_3), 1.6 (sextet, J = 7.5 Hz, 2 H, CH_2CH_3), 2.2–2.6 (m, 6 H, CH_2), 4.8–5.1 (m, 2 H, $CH_2{=}CH$), 5.5–6.0 (m, 1 H, $CH{=}CH_2$); ^{13}C NMR (25.034 MHz, $CDCl_3$) δ 13.8 (C-1), 17.3 (C-2), 27.8 (C-3), 41.8 and 44.8 (C-5 and C-6), 115.1 (C-8), 137.2 (C-7), 210.1 (C-4).

7-Octen-4-one Oxime. To a stirred solution of 5 g (72 mmol) of hydroxylamine hydrochloride and 5 g (47 mmol) of sodium carbonate in 300 mL of methanol was added 5.37 g (43 mmol) of ketone **5**. The mixture was heated at reflux for 8 h and then stirred an additional 12 h. The solution was concentrated to ca. 50 mL and filtered through a glass fritted funnel. The filtrate was then diluted with dry ether and washed (water and brine). The resulting solution was dried over $MgSO_4$, filtered, concentrated, and evaporatively distilled (1.0 mm, 78 °C) to yield 5.77 g (96% yield) of pure oxime as a mixture of two stereoisomers (ca. 1:1): IR (film) 3260, 1644, 1455, 915, 995 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.8–1.1 (overlapping triplets, 3 H, CH_3), 1.3–1.8 (m, 2 H, CH_2), 2.1–2.6 (m, 6 H, CH_2), 4.9–5.2 (m, 2 H, $CH_2{=}CH$), 5.6–6.1 (m, 1 H, $CH{=}CH_2$), 9.1 (br s, 1 H, OH); ^{13}C NMR (25.034 MHz, $CDCl_3$) δ 13.8 and 14.3 (C-1), 19.1 and 19.5 (C-2), 27.0, 29.6, 29.7, 30.3, 33.5, and 36.3 (C-3, C-5, and C-6), 115.0 and 115.2 (C-8), 137.5 and 137.7 (C-7), 160.9 (C-4).

4-[(Carbobenzyloxy)amino]-7-octene (6). A solution of the above oxime (930 mg, 6.6 mmol) in 10 mL of dry ether was added dropwise under N_2 to a brine/ice chilled, magnetically stirred solution of lithium aluminum hydride (1 g, 264 mmol) in 50 mL of dry ether. The ice bath was removed, and the system was equipped with a condenser. The mixture was heated at reflux for 18 h under N_2, chilled in a brine/ice bath, and hydrolyzed by dropwise addition of 1 mL of H_2O, 1 mL of 15% NaOH, and then 3 mL of H_2O. The mixture was stirred for 8 h at room temperature and then treated with 2 mL (18 mmol) of benzyl chloroformate and stirred for an additional 8 h. The resulting mixture was filtered, washed (bicarbonate, water, brine), dried over $MgSO_4$, filtered, and concentrated. Microdistillation (110 °C, 1.0 mm) followed by a wash through a silica column with ether gave 1.63 g (95% yield) of carbamate **6**: mp 52–53 °C; IR (film) 3325 (NH), 1695 (C=O), 1538, 994 and 910 (C=C), 735, 696 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.9 (t, J = 6.7 Hz, 3 H, CH_3), 1.2–1.7 (m, 6 H), 2.1 (br q, J = 8.4 Hz, 2 H, allylic CH_2), 3.5–3.8 (m, 1 H, methine), 4.6 (br d, J = 8.8 Hz, 1 H, NH), 4.9–5.2 (m, 2 H, $H_2C{=}CH$), 5.1 (s, 2 H, OCH_2Ph), 5.7–6.0 (m, 1 H, $HC{=}CH_2$), 7.3 (br s, 5 H, phenyl); ^{13}C NMR (25.034 MHz, $CDCl_3$) δ 13.5 (C-1), 18.6 (C-2), 29.8 (C-3), 34.2 and 37.1 (C-5 or C-6); 50.3 (C-4), 65.8 (OCH_2), 114.1 (C-7), 127.3, 127.9, and 136.5 (phenyl), 137.7 (C-8), 155.9 (C=O).

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.45; H, 9.01; N, 5.28.

***trans*-*N*-(Carbobenzyloxy)-2-propyl-5-(iodomethyl)pyrrolidine (7b).** To a magnetically stirred solution of mercuric acetate (4 g, 12.6 mmol) in 150 mL of tetrahydrofuran was added, in one portion, 1.6 g (5.0 mmol) of carbamate **6**. The solution was stirred at room temperature for 18 h and then concentrated. The resulting alkylmercuric acetate **7a** was dissolved in 150 mL of acetone and treated with 8 g (48.2 mmol) of potassium iodide. The flask was wrapped in aluminum foil and magnetically stirred for 12 h. The resulting solution was concentrated, and 100 mL of ether and 25 mL of water were added. The layers were separated, and the ether was washed (water and brine), dried, filtered, and concentrated to yield the crude alkylmercury iodide. This material was dissolved in 150 mL of dry CH_2Cl_2 under nitrogen, placed in an ice/brine bath, and treated, with stirring, with 1.85 g (7.3 mmol) of iodine. The flask was removed from the ice bath, wrapped in aluminum foil, allowed to warm slowly to room temperature, and stirred for an additional 10 h. The solution was decanted away from the mercuric iodide solids, concentrated, and chromatographed on silica gel with CH_2Cl_2 to yield 1.84 g (78% yield) of alkyl iodide **7b**: IR (film) 1755, 1698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.8 and 0.9 (overlapping triplets, carbamate rotation slow, J = 7.0 Hz, 3 H, CH_3), 1.1–2.2 (m, 8 H, 4 CH_2), 2.94 and 3.12 (t, J = 9.5 Hz, 1 H, CH_aHI), 3.4 and 3.65 (dd, J = 9.5 and 2.4 Hz, 1 H, CH_bHI), 3.8–4.0 (m, 1 H, C-2 methine), 4.0–4.2 (m, 1 H, C-5 methine), 5.1–5.3 (m, 2 H, OCH_2Ph), 7.2 (br s, 5 H, phenyl), off-resonance decoupling was used to corroborate the above assignments; ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 8.7 (CH_2I), 13.8 (CH_3), 19.6 (CH_2CH_3), 26.1, 27.2, 28.0, 28.5, 34.5, and 35.9 (C-3, C-4, and CH_2Et), 58.6 and 59.0 (C-2 or C-5), 58.7 (C-2 or C-5), 66.6 (OCH_2), 127.8, 128.4, and 136.5 (phenyl), 153.7 and 154.3 (C=O).

***trans*-2-Propyl-5-(iodomethyl)pyrrolidine Hydrobromide.** To a mixture of 1.1 g (2.8 mmol) of iodide **7b** and 1.5 mL of glacial acetic acid under N_2 in a magnetically stirred flask was added 1.5 mL of glacial acetic acid, which had been previously saturated with anhydrous hydrogen bromide. The flask was purged with anhydrous hydrogen bromide and stoppered for 16 h, and then 300 mL of dry diethyl ether was added in one portion. Filtration yielded 804.6 mg (84% yield) of white crystals: mp 157–159 °C; IR ($CHCl_3$) 2300–3200 (NH_2^+) cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 0.8 (t, J = 7.4 Hz, 3 H, CH_3), 1.3 (sextet, J = 7.4 Hz, 2 H, CH_2CH_3), 1.5–1.8 (m, 4 H), 2.1–2.3 (m, 2 H), 3.3 (dd, J = 11.1 and 14.8 Hz, 1 H, CH_aHI), 3.45 (dd, J = 7.1 and 14.8 Hz, 1 H, CH_bHI), 3.6 (m, 1 H, C-2 methine), 3.85 (m, 1 H, C-5 methine); ^{13}C NMR (50.31 MHz, D_2O) δ 2.8 (CH_2I), 13.3 (CH_3), 19.6 (CH_2CH_3), 31.1, 31.7, and 34.1 (C-3, C-4, and CH_2Et), 61.4 and 61.5 (C-2 and C-5).

Anal. Calcd for $C_8H_{15}NBrI$: C, 28.76; H, 5.13; N, 4.19. Found: C, 28.95; H, 5.17; N, 4.21.

***2-exo*-Propyl-1-azabicyclo[3.1.0]hexane (8a).** A magnetically stirred solution of the above hydrobromide (100 mg, 0.30 mmol) in 5 mL of H_2O was treated with 100 mg (0.94 mmol) of sodium carbonate. The mixture was stirred for 1 h, then $CDCl_3$ was added,

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and the aqueous layer was saturated with sodium chloride. The layers were separated, and the aqueous layer was extracted three times with $CDCl_3$. The $CDCl_3$ portions were combined, dried with anhydrous K_2CO_3, and filtered through a glass fritted funnel containing a plug of anhydrous K_2CO_3. Samples of the aziridine in other organic solvents were prepared by extraction from the aqueous layer with the desired solvent. ^1H NMR (90 MHz, $CDCl_3$) δ 0.9 (t, J = 6.3 Hz, 3 H, CH_3), 1.0–1.7 (m, 8 H), 1.7–2.0 (m, 2 H, aziridine CH_2), 2.2–2.4 (m, 1 H, C-5 methine), 2.8–3.1 (m, 1 H, C-2 methine); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 14.2 (CH_3), 20.0 (CH_2CH_3), 24.4, 24.5, and 27.4 (C-3, C-4, and CH_2Et), 38.9 (C-6), 39.1 (C-5), 63.8 (C-2).

Ring-Opening Reactions of Aziridine 8a. A. Reaction with Excess Trifluoroacetic Acid. To a magnetically stirred solution of aziridine **8a** in dichloromethane at −78 °C was added an excess of trifluoroacetic acid. The solution was allowed to warm to room temperature, stirred overnight, concentrated, and dissolved in D_2O for ^1H NMR analysis, which showed the presence of only pyrrolidine **9** (R = $CH_2CH_2CH_3$, Y = OH): ^1H NMR (90 MHz, D_2O) δ 0.8 (t, J = 6.3 Hz, 3 H, CH_3), 1.0–2.2 (m, 8 H), 2.5–2.8 (m, 2 H, CH_2OH), 3.3–3.7 (m, 2 H, C-2 and C-5 H). The same result was obtained by treatment of a D_2O solution of **8a** with excess trifluoroacetic acid at room temperature. Reaction in $CDCl_3$ at room temperature or in hexane at −78 °C gave material that contained small amounts (less than 20%) of six-membered-ring product.

B. Slow Addition of Trifluoroacetic Acid. To a magnetically stirred solution of **8a** in hexane was added ca. 1 equiv of trifluoroacetic acid in 10 mL of hexane, one drop at a time, over a 2-h period. The solution was stirred overnight, treated with additional trifluoroacetic acid, concentrated, dissolved in D_2O, and extracted with hexane. Analysis of the D_2O layer by ^1H NMR indicated the presence of six- and five-membered products (**14** and the corresponding pyrrolidine trifluoroacetamide (**11**, R = $CH_2CH_2CH_3$, Y = OH))[10] in a ratio of ca. 15:85: ^1H NMR (90 MHz, D_2O, signals characteristic of **14**) δ 1.6 (t, J = 11.7 Hz, C-6 H_a), 3.0 (m, C-2 H), 3.3 (dd, J = 11.7 and 4.5 Hz, C-6 H_e), 3.4–4.0 (m, C-5 H). Low-resolution MS of material after mild treatment with sodium carbonate solution indicated presence of a trifluoroacetyl group, m/e (M^+) 239.2 (calcd 239.235).

2-*exo*-Methyl-1-azabicyclo[3.1.0]hexane (8b). This aziridine was prepared from amidomercuration product **3** by the same series of steps used to convert **7a** to **8a**. To a magnetically stirred solution of pyrrolidine derivative **3**,[1] prepared from 1.0 g (4.3 mmol) of **2**, in acetone was added 4.6 g (5.6 equiv) of potassium iodide. The mixture was stirred for 12 h, concentrated, and diluted with water and ether. The layers were separated, and the aqueous layer was extracted three times with ether. The combined ether extracts were dried, filtered, and concentrated. The resulting crude alkylmercury iodide was then dissolved in dried methylene chloride, chilled to −20 °C, and treated, with stirring, with 1.3 g (1.2 equiv) of iodine. After the mixture had been stirred at −20 °C for 1h, it was allowed to warm to room temperature and stirred for an additional 12 h. The solution was decanted from the red mercuric iodide crystals, washed (sodium thiosulfate, water, brine), dried, filtered, and concentrated. The crude alkyl iodide was purified by chromatography on silica gel with hexane/ether (80:20) to give 1.25 g (81%) of the pure alkyl iodide: ^1H NMR (200 MHz, $CDCl_3$) δ 1.11 and 1.18 (d, J = 6.3 Hz, 3 H, CH_3, carbamate rotation slow), 1.5 (m, 1 H), 1.9–2.2 (m, 3 H), 2.94 (t, J = 9.6 Hz, CH_aHI) and 3.09 (t, J = 9.4 Hz, CH_aHI, other rotamer), 3.38 (dd, J = 9.6 and 1.7 Hz, CH_bHI) and 3.60 Hz (dd, J = 9.4 and 2.5 Hz, CH_bHI, other rotamer), 4.0–4.2 (m, 2 H, C-2 and C-5 H), 5.1 (m, 2 H, OCH_2Ph), 7.3 (s, 5 H, phenyl); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 8.6 and 8.7 (CH_2I, signals for two carbamate rotamers), 19.0 and 20.2 (CH_3), 27.5, 28.1, 29.0, and 29.9 (C-3 and C-4), 54.0 and 54.4 (C-2 or C-5), 58.7 and 58.8 (C-2 or C-5), 66.4 and 66.5 (OCH_2Ph), 127.6, 127.7, 127.8, and 128.3 (aromatic), 136.4 and 136.5 (quaternary aromatic), 153.5 and 154.2 (C=O).

The alkyl iodide (425 mg, 1.18 mmol) was dissolved in 0.5 mL of acetic acid and treated with 1 mL of acetic acid which had been previously saturated with anhydrous hydrogen bromide. The flask was sealed, stirred for 48 h, diluted with dry ether, and allowed to stand in the refrigerator. The white needlelike crystals of *trans*-2-methyl-5-(iodomethyl)pyrrolidine hydrobromide were isolated by filtration through a glass fritted funnel, yielding 317 mg (88% yield): ^1H NMR (200 MHz, D_2O) δ 1.2 (d, J = 6.7 Hz, 3 H, CH_3), 1.5–2.3 (m, 4 H, CH_2), 3.21 (dd, J = 8.4 and 11.2 Hz, 1 H, CH_aHI), 3.37 (dd, J = 5.0 and 11.2 Hz, 1 H, CH_bHI), 3.6–3.75 (m, 1 H), 3.75–3.9 (m, 1 H); ^{13}C NMR (50.31 MHz, D_2O) δ 2.8 (CH_2I), 17.0 (CH_3), 31.6 and 32.4 (C-3 and C-4), 57.1 and 61.4 (C-2 and C-5).

A magnetically stirred solution of the hydrobromide in water was treated with at least 4 equiv of sodium carbonate to form aziridine **8b**. The aqueous layer was saturated with sodium chloride and extracted into an organic solvent, dried with anhydrous K_2CO_3, and filtered to yield aziridine **8b**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.1 (d, J = 6.8 Hz, 3 H, CH_3), 1.2 (m, 1 H, C-6 H), 1.2–1.4 (m, 1 H, C-3 H), 1.5–1.7 (m, 2 H, C-3 and C-6 H), 1.9–2.1 (m, 2 H, C-4 CH_2), 2.4 (m, 1 H, C-5 H), 3.2 (quintet, J = 6.8 Hz, C-2 H); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 22.5 (CH_3), 24.0, 25.8, and 27.1 (C-3, C-4, and C-6), 38.9 (C-5), 58.8 (C-2).

Ring-Opening Reactions of Aziridine 8b. A. Reaction with Trifluoroacetic Acid. Excess trifluoroacetic acid was added to a solution of aziridine **8b** in D_2O. ^1H NMR of the mixture indicated the presence of only the five-membered ring product **9** (R = CH_3, Y = Cl): ^1H NMR (D_2O, 200 MHz) δ 1.2 (d, J = 7.2 Hz, 3 H, CH_3), 1.6–2.4 (m, 4 H, CH_2), 2.55 (dd, J = 4.1 and 6.0 Hz, 1 H, CH_aHOH), 2.75 (dd, J = 4.1 Hz and 7.4 Hz, 1 H, CH_eHOH), 3.6 (br q, 1 H, C-5 H), 3.8 (br quint, 1 H, C-2 H), decoupling experiments showed that the signal at δ 3.6 is coupled to the signals at δ 2.55 and 2.75.

B. Reaction with HCl. A solution of aziridine **8b** in $CDCl_3$ was treated with an excess of anhydrous HCl over a 1-min period. The mixture was stirred for 1 h and analyzed by ^1H NMR, which indicated the presence of a 62:38 mixture of **9b** and **10b**. A similar reaction in hexane gave a 29:71 mixture of isomers. A sample of pure **10b** was obtained through a variety of manipulations: ^1H NMR (200 MHz, D_2O) δ 1.2 (d, J = 6.6 Hz, 3 H, CH_3), 1.3–2.3 (m, 4 H), 3.0 (dd, J = 10.8 and 12.5 Hz, 1 H, C-6 H_a), 3.2 (m, 1 H, C-2 H), 3.55 (ddd, J = 1.8, 4.4, and 12.5 Hz, 1 H, C-6 H_e), 4.07 (tt, J = 4.4 and 10.8 Hz, 1 H, C-5 H). Signals for the five-membered-ring product **9b** are observed at δ 1.17 (d, J = 6.6 Hz, CH_3) and 3.5–4.0 (m).

Equilibration of 9b and 10b. A mixture of **9b** and **10b**, prepared as described above, was dissolved in D_2O and treated with ca. 1 equiv of sodium bicarbonate. The solution was saturated with NaCl and extracted with ether (three times). The combined ether fractions were dried over K_2CO_3, filtered, and allowed to stand at room temperature for 5 h. Treatment with excess anhydrous hydrogen chloride, concentration, and analysis by ^1H NMR showed the presence of a mixture of **9b** and **10b** in a ratio of 14:86 irrespective of the ratio of isomers in the starting material.

(±)-Pseudoconhydrine (1). A hexane solution of aziridine **8a**, prepared from 100 mg (0.30 mmol) of *trans*-2-propyl-5-(iodomethyl)pyrrolidine hydrobromide, was magnetically stirred at room temperature as 1 equiv (22 μL, 0.30 mmol) of trifluoroacetic acid was added over a period of 4 h. The mixture was stirred for 1 h and then an additional 50 μL of trifluoroacetic acid was added over a 1-h period. The solution was concentrated, dissolved in 100 mL of methanol, treated with 200 mg (1.88 mmol) of sodium carbonate, and stirred for 1.5 h. The resulting mixture was concentrated, and the residue was washed with three portions of dichloromethane. The solutions were filtered, combined, concentrated, and evaporatively distilled (1.0 mm, 80 °C) into a 20 cm × 10 mm Pyrex tube of which the portion nearest the oven was heated to 55–60 °C by an asbestos strip heater. This resulted in the separation of white crystals in the hotter portion of the tube from a clear oil in the cooler portion. The clear oil amounting to 5.3 mg (12% yield) consisted of a mixture of products, the major one being *trans*-2-propyl-5-hydroxymethylpyrrolidine. The crystals were removed from the tube by dissolution with dichloromethane. Redistillation gave 21.5 mg (50% yield) of pure (±)-pseudoconhydrine: mp (sealed capillary under N_2) 89.5–90.5 °C (lit. mp 90–92 °C,[2b] 91.5–92 °C[2c]); IR ($CHCl_3$) 3605, 3330, 3180, 1448, 1060 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 0.75 (br t, J = 6.4 Hz, 3 H, CH_3), 0.9–1.3 (m, 6 H), 1.7 (dq, J = 12.8 and ca. 3 Hz, 1 H, C-3 H_e), 1.9 (dm, J = ca. 11 Hz, 1 H, C-4 H_e), 2.24 (dd, J = 10.7 and 11.4 Hz, 1 H, C-6 H_a), 2.2–2.4 (m, 1 H, C-2 H), 2.95 (ddd, J = 2.3, 4.8, and 11.4 Hz, C-6 H_e), 3.5 (m, 1 H, C-5 H), above assignments were made with aid of decoupling experiments; ^{13}C NMR (50.31 MHz, D_2O) δ 13.8 (CH_3), 19.1

(CH_2CH_3), 30.3, 32.9, and 37.8 (C-3, C-4, and CH_2Et), 52.0 (C-6), 55.0 (C-2), 67.8 (C-5); mass spectrum (M^+), calcd for $C_8H_{17}NO$ 143.130995, found 143.130559.

A deuteriochloroform solution containing 7 mg of (±)-pseudoconhydrine was treated with excess anhydrous hydrogen chloride. The resulting milky solution was concentrated, and the crystals were recrystallized from EtOH/EtOAc to give (±)-pseudoconhydrine hydrochloride: mp 157.0–157.5 °C (lit.[2b] mp 135–140 °C); ^1H NMR (200 MHz, D_2O) δ 0.79 (t, J = 7.2 Hz, 3 H, CH_3), 1.1–1.6 (m, 6 H), 1.9–2.1 (m, 2 H), 2.2–2.4 (dd, J = 11.6 and 4.3 Hz, 1 H, C-6 H_e), 2.65 (t, J = 11.6 Hz, 1 H, C-6 H_a), 3.0 (m, 1 H, C-2 methine), 3.8 (m, 1 H, C-5 methine); ^{13}C NMR (20 MHz, D_2O) δ 13.8 (CH_3), 18.9 (CH_2CH_3), 26.2, 30.3, and 34.6 (C-3, C-4, and CH_2Et), 49.3 (C-6), 56.4 (C-2), 63.8 (C-5).

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Registry No. (±)-1, 5457-27-2; (±)-1·HCl, 41221-92-5; (±)-2, 87830-46-4; (±)-3, 87830-47-5; (±)-4, 87830-31-7; 5, 30503-12-9; (*E*)-5 oxime, 87830-32-8; (*Z*)-5 oxime, 87830-48-6; (±)-6, 87830-33-9; (±)-7a, 87830-45-3; (±)-7b, 87830-34-0; (±)-8a, 87830-36-2; (±)-8b, 87830-40-8; (±)-9·F_3CCO_2 (R = $CH_2CH_2CH_3$; Y = OH), 87830-38-4; (±)-9·F_3CCO_2 (R = CH_3; Y = Cl), 87830-43-1; (±)-10b·Cl, 87830-44-2; (±)-11 (R = $CH_2CH_2CH_3$; Y = OH), 87830-37-3; (±)-11·HBr (R = $CH_2CH_2CH_3$; Y = I), 87830-35-1; (±)-11·HBr (R = CH_3; Y = I), 87830-41-9; (±)-14, 87830-39-5; 4-bromobutene, 5162-44-7; butyraldehyde, 123-72-8; benzyl chloroformate, 501-53-1.

Stereochemistry and Regiochemistry of Electron Impact, Photolytically, and Thermally Induced Eliminations from 5α-Cholestanyl Acetates

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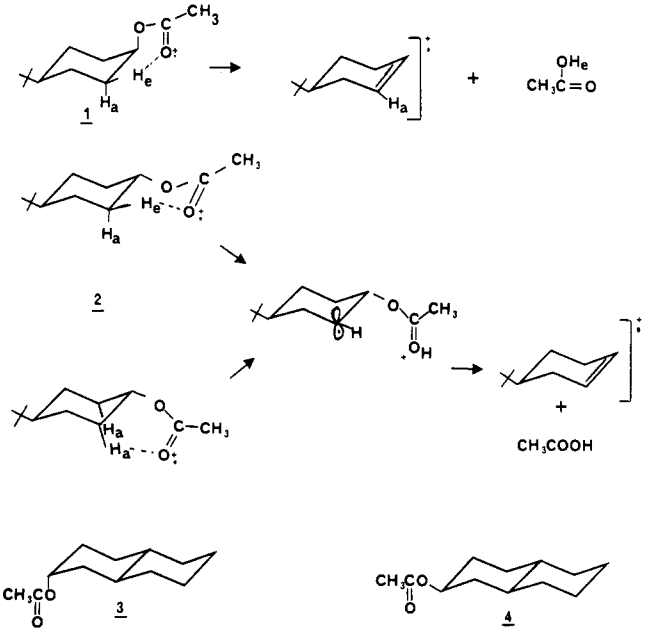
Deuterium-labeled compounds were used to define the stereochemistry and regiochemistry of the electron impact induced eliminations of acetic acid from 5α-cholestanyl 3α-acetate, 4α-acetate, and 6α-acetate. Comparison of the electron impact induced eliminations to the pyrolysis and to the photolysis of the corresponding phenylacetates confirmed that the mass spectral elimination was a stepwise process proceeding through the stable chair conformation of the steroid's cyclohexyl ring. The equatorially oriented 4α- and 6α-acetates fragmented with predominant loss of a secondary trans-equatorial hydrogen, rather than the tertiary cis-axial hydrogen, despite the a priori greater migratory aptitude of tertiary hydrogens. The electron impact induced fragmentation of the 3α-acetate occurred with predominant loss of a C-4 hydrogen; in contrast, the photolysis of the corresponding 3α-phenylacetate results in loss of a C-2 hydrogen. This result can be attributed to the reversibility of the photolytically induced hydrogen-abstraction step.

Steroids are particularly useful as substrates for the investigation of the regiochemistry and stereochemistry of electron impact induced fragmentations. Internuclear distances and angles are well-defined, and the precursors necessary to produce regiospecifically and/or stereospecifically labeled molecules are often readily available. Further, the solution chemistry behaviors and properties of these molecules are comparatively well studied and understood, facilitating the interpretation of results obtained in mass spectrometric studies. Thus, steroid acetates are the focus to the current study on electron impact induced elimination of acetic acid from unsymmetrical derivatives.

It has already been demonstrated that the electron impact induced loss of acetic acid from axially oriented symmetrically substituted cyclohexyl acetates (e.g., *cis*-4-*tert*-butylcyclohexyl acetate, 1, Scheme I) proceeds with predominant loss of a cis-equatorial hydrogen,[1] consistent with hydrogen abstraction from the most stable chair conformer and the requirement for approach of the abstracting oxygen atom within 1.8 Å of the itinerant hydrogen.[2] More surprisingly, it has also been demonstrated that equatorially oriented symmetrically substituted cyclohexyl acetates (e.g., *trans*-4-*tert*-butylcyclohexyl acetate, 2) fragments with predominant loss of a trans-equatorial hydrogen atom.[1] This result is also consistent with hydrogen abstraction from the most stable chair conformer,

Scheme I



provided that the fragmentation is a stepwise process. Then, the unfavorable 1,3-diaxial-like interaction between

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