THE JOURNAL OF Organic Chemistry

VOLUME 52, NUMBER 9

MAY 1, 1987

Synthesis and Reactivity of 6- and 7-Methoxyindano[1,2-*b*]aziridines

Nim Ming Nguy,[1] I.-C. Chiu, and Harold Kohn*

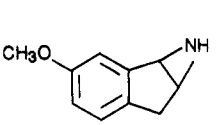
Department of Chemistry, University of Houston, Houston, Texas 77004

Received October 27, 1986

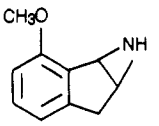
The synthesis, spectral, and reactivity properties of 6-methoxy- and 7-methoxyindano[1,2-*b*]aziridines (**8** and **9**, respectively) are detailed. Hydrolysis of each aziridine produced the corresponding *trans*- and *cis*-2-amino-1-indanols in approximately 1:2 ratio, respectively. The 7-methoxy adduct **9** underwent hydrolysis approximately 250 times faster than the isomeric 6-methoxyaziridine **8** at pH 8.88. Both the product profiles and the kinetic rate data for the hydrolysis of **8** and **9** are consistent with a mechanism in which protonation of the aziridine precedes the rate-determining ring-opening step to generate the corresponding benzylic cation. The products generated in these reactions paralleled those reported for the hydrolysis of the antineoplastic agent mitomycin C under reductive conditions. The implications of these findings in relation to the mode of action of mitomycin C are discussed.

Mitomycin C (**1**) is a potent antitumor agent of significant clinical importance.[2] Suggestions have been made that mono-(C-1) and di-(C-1 and -10) functional binding of an activated form of **1** with DNA proceeds by either a stepwise (S_N1 type) or a direct substitution (S_N2) process.[3-9] Recent in vitro product studies have indicated that nucleophilic substitution reactions at carbons 1 and 10 in reductively activated **1** proceed in a *stepwise* fashion.[4-8] In 1981, Moore and Czerniak proposed that the C-8 hydroxyl moiety in **3** triggers aziridine ring cleavage by proton loss to produce the quinone methide **4**[3b] (Scheme I).[10] This process can also be facilitated by conjugative interaction of the lone pair of electrons on the hydroxyl group to furnish **5**. Only indirect evidence exists on behalf of this notion.[6a,7a]

In this paper, the synthesis and reactivity of 6-methoxy (**8**) and 7-methoxy (**9**) indano[1,2-*b*]aziridines are described. Compounds **8** and **9** contain an aromatic ring



8



9

adjacent to the aziridine moiety. A similar situation prevails in the reductively activated mitosene species **3**. Significantly, in **9** and **3** but not in **8**, the lone pair of electrons on the phenolic oxygen atom can facilitate aziridine ring cleavage. The results obtained for **8** and **9** are consistent with the hypothesis that the carbon-8 hy-

(1) Abstracted from the Masters dissertation of this author. Additional structure proof and experimental and spectral data may be found in this reference.

(2) (a) Carter, S. K.; Crooke, S. T. *Mitomycin C. Current Status and New Developments*; Academic: New York, 1979. (b) Remers, W. A. *The Chemistry of Antitumor Antibiotics*; Wiley: New York, 1979; Vol. 1, pp 221-276.

(3) (a) Szybalski, W.; Iyer, V. N. In *Antibiotics, Mechanism of Action*; Gottlieb, D., Shaw, P. D., Eds.; Springer: New York, 1967; Vol. 1, pp 211-245. (b) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249 and references therein.

(4) Bean, M.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 5033-5041. (b) Bean, M.; Kohn, H. Ibid. **1985**, *50*, 293-298.

(5) (a) Hornemann, U.; Keller, P. J.; Kozlowski, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 7121-7124. (b) Hornemann, U.; Iguchi, K.; Keller, P. J.; Kozlowski, J. F.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 5026-5033.

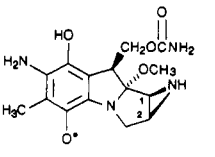
(6) Kohn, H.; Zein, N. *J. Am. Chem. Soc.* **1983**, *105*, 4105-4106. (b) Zein, N.; Kohn, H. Ibid. **1986**, *108*, 296-297.

(7) (a) Tomasz, M.; Lipman, R.; Verdine, G. L.; Nakanishi, K. *Biochemistry* **1986**, *25*, 4337-4344. (b) Tomasz, M.; Lipman, R. Ibid. **1981**, *20*, 5056-5061 and references therein.

(8) Andrews, P. A.; Pan, S.-S.; Bachur, N. R. *J. Am. Chem. Soc.* **1986**, *108*, 4158-4166.

(9) Rebek, J.; Shaber, S. H.; Sue, Y.-K.; Gehret, J.-C.; Zimmerman, S. *J. Org. Chem.* **1984**, *49*, 5164-5174.

(10) In Scheme I, **1** is envisioned to undergo reduction to the hydroquinone **2**. Alternatively, initial reduction may furnish the semiquinone **i** (or the corresponding conjugate base). Both types of intermediates are consistent with results observed in this study. For recent studies, stressing the importance of the semiquinone species, please see: (a) Pan, S.-S.; Andrews, P. A.; Glover, C. J.; Bachur, N. R. *J. Biol. Chem.* **1984**, *259*, 959-966. (b) Danishefsky, S. J.; Egbertson, M. *J. Am. Chem. Soc.* **1986**, *108*, 4648-4650. (c) Kohn, H.; Zein, N.; Lin, X. Q.; Ding, J.-Q.; Kadish, K. M. *J. Am. Chem. Soc.*, in press.



0022-3263/87/1952-1649$01.50/0

Scheme I

droxyl group in **3** plays a critical role in the aziridine ring-opening step.

Synthesis

The pathways employed for the preparation of 6-methoxy (**8**) and 7-methoxy (**9**) indano[1,2-*b*]aziridines are outlined in Schemes II and III, respectively. In both instances, established procedures[11-16] were used to prepare the central intermediates **17** and **25**. Introduction of the aziridine moiety was then accomplished by treatment of the appropriate indene (**17**, **25**) with *N*-bromosuccinimide and sodium azide[17,18] to furnish the bromoazide (**18**, **26**), followed by reductive cyclization with either lithium aluminum hydride or lithium tri-*tert*-butoxyaluminohydride.

In both synthetic series, the major product isolated in the *N*-bromosuccinimide–sodium azide step was the desired bromo azide [**18** (51% yield), **26** (40% yield)]. An unidentified adduct was also obtained in the 6-methoxyindene reaction, while both 7-methoxy-*trans*-2-azido-1-bromoindan (**27**) and 7-methoxy-*trans*-2-bromo-1-indanol (**28**) were isolated in the 7-methoxyindene reaction. The identity of **18**, **26**, **27**, and **28** were supported by their spectral properties. Each of the three bromo azides (**18**, **26**, and **27**) exhibited a discernible molecular ion peak in the mass spectrum, as well as a strong absorption in the

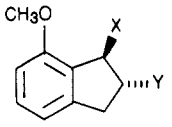
Scheme II. Synthesis of 6-Methoxyindano[1,2-*b*]aziridine (8)[a]

[a] (a) KNO_3, H_2SO_4;[11] (b) (i) $SnCl_2 \cdot H_2O$, CH_3CH_2OH, (ii) separation (Et_2O extraction);[11] (c) $NaNO_2$, H_2SO_4;[11] (d) K_2CO_3, CH_3I, acetone;[11] (e) $NaBH_4$, CH_3OH;[12] (f) *p*-TSA, benzene;[13] (g) NaN_3, NBS, DME–H_2O; (h) $LiAlH_4$, Et_2O; (i) PPA.[14]

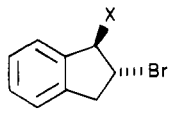
Scheme III. Synthesis of 7-Methoxyindano[1,2-*b*]aziridine (9)[a]

[a] (a) 3-Chloropropionyl chloride, $POCl_3$;[15] (b) $AlCl_3$;[15,16] (c) K_2CO_3, CH_3I, acetone;[11] (d) $NaBH_4$, CH_3OH;[12] (e) *p*-TSA, benzene;[12,13] (f) NaN_3, NBS, DME–H_2O; (g) $LiAlH(O\text{-}t\text{-}Bu)_3$, Et_2O.

(11) Ingold, C. K.; Piggot, H. A. *J. Chem. Soc.* **1923**, 1469–1509.
(12) Winter, J. C.; Godse, D. D.; Gessner, P. K. *J. Org. Chem.* **1965**, *30*, 3231–3233.
(13) Tortai, J.-P.; Marechal, E. *Bull. Soc. Chim. Fr.* **1971**, *7*, 2673–2688.
(14) Uhlig, F. *Angew. Chem.* **1954**, *15*, 435–436.
(15) (a) Huneck, S.; Schreiher, K. *Phytochemistry* **1977**, *16*, 1013–1016. (b) Mayer, F.; van Zutphen, L. *Chem. Ber.* **1924**, *57*, 200–202.
(16) Bruce, D. B.; Sorrie, A. J. S.; Thomson, R. H. *J. Chem. Soc.* **1953**, 2403–2406.
(17) Hassner, A.; Fowler, F. W. *J. Org. Chem.* **1968**, *33*, 2686–2691. Hassner, A.; Matthews, G. J.; Fowler, F. W. *J. Am. Chem. Soc.* **1969**, *91*, 5046–5053.
(18) Chiu, I.-C.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 2857–2866.



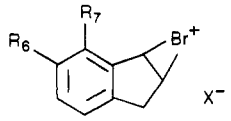
27 X = Br, Y = N_3
28 X = OH, Y = Br



29 X = N_3
30 X = OH

infrared spectrum at 2100 cm^{-1} for the azido group.[19,20] Furthermore, the ^1H (H_1, H_2, $H_{3\alpha}$, $H_{3\beta}$) and ^{13}C (C_1, C_2, C_3) NMR chemical shift values obtained for **18** and **26** compared favorably to those previously reported for the parent bromo azide **29**.[18] Likewise, excellent agreement existed in the ^1H and ^{13}C NMR spectral properties observed for **28** and those obtained for 2-bromo-1-indanol (**30**).[21,22]

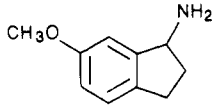
Formation of **18** and **26** is envisioned to occur by nucleophilic attack by azide ion at C-1 of bromonium ions **31** and **32**, respectively. Correspondingly, competitive



31 R_6 = OCH_3, R_7 = H
32 R_6 = H, R_7 = OCH_3

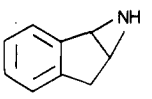
substitution by water at C-1 in **32** would yield **28**, while attack by azide ion at C-2 would furnish **27**. The production of **27** is supported by the recent findings of Sivasubramanian and co-workers.[23] These investigators reported the formation of 2-azido-1-iodo-1-arylcyclohexanes from 1-arylcyclohexenes and iodine azide.

The critical step in both synthetic sequences was the reductive ring closure of bromo azides **18** and **26** to aziridines **8** and **9**, respectively. Indano[1,2-*b*]aziridines **8** and **9** proved to be *highly reactive* and demanded considerable care in their preparation, purification, and storage (see Experimental Section and ref 1 for details). Treatment of **18** with lithium aluminum hydride at 0 °C (45 min) and then at room temperature (45 min) furnished the desired aziridine **8** in 75% yield. Longer reaction times yielded 6-methoxy-1-aminoindan (**33**).



33

Use of similar reductive conditions for the conversion of **26** to **9** proved unsuccessful. Our inability to isolate the desired aziridine in these reactions led us to utilize the milder reducing agent lithium tri-*tert*-butoxyaluminohydride[24] in refluxing ether. TLC analysis after 24 h indicated the presence of a new compound along with substantial amounts of starting material **26**. Due to the anticipated lability of the product, the reaction was quenched, worked-up, and carefully purified by flash column chromatography. Steps were instituted at each stage of the purification process in order to minimize the loss (i.e., decomposition, reaction) of the aziridine. Despite these precautions the estimated yield (^1H NMR analysis) of **9** was only 1%. The ^1H and ^{13}C NMR and low-resolution mass spectral properties for both **8** and **9** supported their proposed structural assignment.[25] In particular, the proton-decoupled ^{13}C NMR spectrum for **8** and **9** displayed three resonances between 34 and 40 ppm for carbons 1, 2, and 3.[26] Moreover, the observed ^1H and ^{13}C NMR and mass spectral fragmentation patterns for **8** and **9** compared favorably with those secured for indano[1,2-*b*]aziridine (**34**).[18]

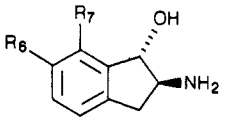


34

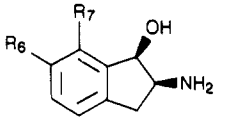
Formation of both **8** and **9** is envisioned to proceed by initial reduction of the azide group to the corresponding amine, followed by intramolecular displacement of bromide to generate the aziridine.[17,27] Correspondingly, the isolation of 6-methoxy-1-aminoindan (**33**) under prolonged reaction times suggested that the initially generated 6-methoxy-1-amino-2-bromoindan underwent further reduction to yield **33**. In support of this notion, lithium aluminum hydride is known to reduce secondary bromides to the corresponding hydrocarbon.[28]

Hydrolysis Products

Dissolution of 6-methoxy (**8**) and 7-methoxy (**9**) indano[1,2-*b*]aziridines respectively in aqueous 2.3 N $HClO_4$ acid led to an approximate 1:4 mixture of the corresponding trans- (**35**, **37**) and cis- (**36**, **38**) 2-amino-1-indanols. The identity of each of these products was secured by their observed NMR spectral properties. In particular, the resonances for carbons 1 and 2 appeared at higher field in the cis adducts (**36** and **38**) than the corresponding signals in the trans compounds (**35** and **37**).



35 R_6 = OCH_3, R_7 = H
37 R_6 = H, R_7 = OCH_3



36 R_6 = OCH_3, R_7 = H
38 R_6 = H, R_7 = OCH_3

The magnitude of these upfield shifts was approximately 6.5 ppm. The direction of this shift was opposite to that generally observed (~0.1 ppm) for the protons bound to these carbons. This inverse relationship as well as the magnitude of these shifts was reported for the simple 2-amino-1-indanols[18,29] and suggests that the values observed for the cis compounds stem from electron density changes due to sterically induced polarization of the carbon–hydrogen bonds (i.e., gauche γ interactions).[30]

Kinetic Studies: Results and Interpretation

The importance of the methoxy group in the hydrolysis of indano[1,2-*b*]aziridines **8** and **9** has been gauged by

(19) Nakanishi, K.; Solomon, P. H. *Infrared Absorption Spectroscopy*, 2nd ed.; Holden-Day: San Francisco, 1977.
(20) Patai, S. *The Chemistry of Functional Groups. The Chemistry of the Azido Group*; Interscience: New York, 1971; pp 3, 195.
(21) (a) Austin, R. A.; Lillya, C. P. *J. Org. Chem.* **1969**, *34*, 1327–1333. (b) Buys, H. R.; Havinga, E. *Tetrahedron* **1968**, *24*, 4967–4979.
(22) Aldrich Chemical Co.
(23) Sivasubramanian, S.; Aravind, S.; Kumarasingh, L. T.; Arumugam, N. *J. Org. Chem.* **1986**, *51*, 1985–1987.
(24) Brown, H. C.; McFarlin, R. F. *J. Am. Chem. Soc.* **1958**, *80*, 5372–5376.
(25) Satisfactory spectra (^1H and ^{13}C NMR, IR, MS, and high-resolution MS) data were obtained for all new compounds prepared in this study except **9**. The ease in which **9** underwent decomposition did not permit the acquisition of the high-resolution mass spectrum data for this compound.
(26) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic: New York, 1972.
(27) Dermer, O. C.; Ham, G. E. *Ethylenimine and Other Aziridines*; Academic: New York, 1969; pp 206–222 and references therein.
(28) Gaylord, N. G. *Reduction with Complex Metal Hydrides*; Interscience: New York, 1956.
(29) Huebner, C. F.; Donoghue, E. M.; Novak, C. J.; Dorfman, L.; Wenkert, E. *J. Org. Chem.* **1970**, *35*, 1149–1154.
(30) Grant, D. M.; Cheney, B. V. *J. Am. Chem. Soc.* **1967**, *89*, 5315–5318. Dalling, D. K.; Grant, D. M. Ibid. **1967**, *89*, 6612–6622.

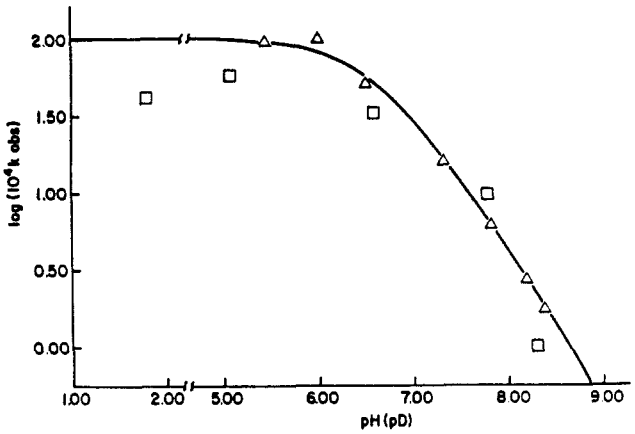


Figure 1. First-order rate constants for the hydrolysis of **8** at 25 °C determined by (△) pH-stat technique and by [□] ^{1}H NMR spectroscopy. The solid curve was obtained by using eq 1, where a = 0.01 s^{-1} and b = 2.41 × 10^{-7} mol L^{-1}.

determining the relative rates of these reactions. Both a pH-stat and a ^{1}H NMR kinetic method were utilized to monitor the conversion of **8** to **35** and **36**. Several experimental details that characterized these studies are worthy of mention (see Experimental Section and ref 1 for additional details.) The pH-stat experiments were conducted in water in the pH range 5.45–8.38. Excellent observed first-order rate constants (Experimental Section, Figure 1) were obtained by using this technique provided the half-lives of the reactions were greater than 40 s. The ^{1}H NMR kinetic experiments were conducted in buffered deuteriated water solutions over the pD range 1.7–8.3.[31] The observed first-order rate constants obtained by this procedure are approximate (Experimental Section, Figure 1). Accurate kinetic information was not secured in these cases due to the relatively long times required to acquire the data points and the need to use high concentrations of buffer solutions. Analyses (^{1}H and TLC) of the product mixtures produced in both sets of experiments indicated the formation of **35** and **36** in an approximate 1:2 ratio, respectively, at all the pH (pD) values studied.

A comparable pH–rate profile for aziridine **9** was not possible. At pH values below 8 hydrolysis of **9** was too rapid to be monitored conveniently by either the pH-stat or the NMR technique. Fortunately, a value for this process was determined at pH 8.88 at 10, 14, and 25 °C (Experimental Section) by using the former method. In all these cases, ring-opening of **9** led to a 1:2 mixture of the amino alcohols **37** and **38**, respectively (TLC and ^{1}H NMR analyses).

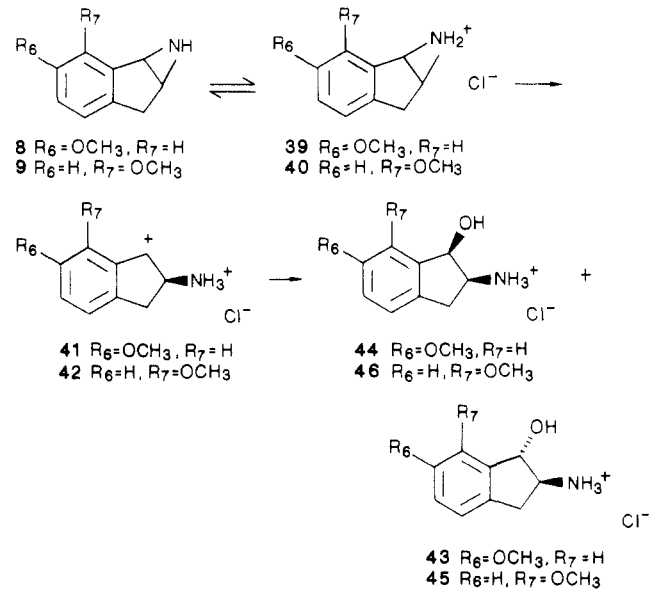
The pH–rate profile (Figure 1) for the hydrolysis of **8** revealed a pH-independent region at low pH (<5) and at higher values a first-order dependency in hydronium ion concentration. A good correlation existed between the measurements observed from the pH-stat method and the data obtained by ^{1}H NMR spectroscopy provided the corrected pD values in the ^{1}H NMR experiments are assumed equivalent to the observed pH values in the pH-stat reactions.[31] The experimental data displayed in Figure 1 can be approximated by the empirical relationship described in eq 1. This relationship as well as the observed

$$k_{obsd} = \frac{a[H^+]}{b + [H^+]} \quad (1)$$

product distribution is consistent with a mechanism in

(31) Bates, R. G. *Determination of pH: Theory and Practice*, 2nd ed.; Wiley: New York, 1973; pp 375–376.

Scheme IV



which protonation of the aziridine (**8** → **39**) precedes the rate-determining ring-opening step to generate the corresponding benzylic carbocation **41** (Scheme IV). The value determined for b (eq 1) from the fit to the kinetic data predicts the dissociation constant (pK_{BH^+}) for **8** to be 6.6. This number is in good agreement with a previous estimate of 6.14 for the dissociation constant of a cyclopenta-fused aziridine.[18]

The isolation of both **37** and **38** in the hydrolysis of **9** provides strong support that a pathway [i.e. (Scheme IV) **9** → **40** → **42** → **45** (**37**) + **46** (**38**)] comparable to that observed for **8** exists in this reaction. Moreover, comparison of the rates of hydrolysis of **8** and **9** predicts that the strategic placement of a methoxy group in the 7-position of the indano[1,2-*b*]aziridine ring system facilitates the rate of ring opening by at least 250-fold. Comparable rate enhancements have been reported for the placement of a methoxy group on an aromatic ring in conjugation with a developing positive charge.[32]

Conclusions

The product and kinetic studies observed for **8** and **9** indicate that hydrolysis of these reactive aziridines proceeds by initial bond breaking at C-1, followed by nucleophilic attack by water at this site. This process is promoted by placement of a methoxy group in conjugation with the developing positive charge at C-1. A comparable role should be provided by the hydroxyl group in the reductively activated mitosene intermediate **3** prior to binding of the drug to a nucleophilic site on DNA (i.e., **3** → **6**).

Experimental Section

General Methods. Melting points were determined with a Thomas-Hoover melting-point apparatus and are uncorrected. Infrared spectra (IR) were run on Perkin-Elmer 1330 or Beckman IR-4250 spectrophotometers and calibrated against the 1601-cm^{-1} band of polystyrene. Ultraviolet spectra (UV) were obtained on a Perkin-Elmer 330 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian Associates Model T60 and FT80A spectrometers or on a Nicolet NT-300 WB

(32) Schubert, W. M.; Keeffe, J. R. *J. Am. Chem. Soc.* **1972**, *94*, 559–566. Modena, G.; Rivetti, F.; Scorrano, G.; Tonellato, U. Ibid. **1977**, *99*, 3392–3395. Vitullo, V. P.; Grabowski, J.; Sridharan, S. *J. Chem. Soc., Chem. Commun.* **1981**, 737–738 and references therein.

spectrometer. C-13 nuclear magnetic resonance (^{13}C NMR) spectra were determined on Varian Associates FT80A or on Nicolet NT-300 WB spectrometers. Chemical shifts (δ) are in parts per million (ppm) relative to Me_4Si, and coupling constants (J values) are in hertz. Mass spectral data (MS) were obtained at an ionizing voltage of 70 eV on a Hewlett-Packard 5930 gas chromatograph–mass spectrometer. High-resolution mass spectra were performed by Dr. John Chinn at the Department of Chemistry, University of Texas at Austin, on a CEC21-110B double-focusing magnetic-sector spectrometer at 70 eV. Exact masses were determined by peak matching. pH-stat measurements were determined with a radiometer assembly consisting of a PHM26 pH meter, a TTT60 titrator, an ABU12 autoburet, and an REC61 Servograph-REA160 recorder.

All reactions were run under nitrogen, and all glassware was dried before use unless noted. The solvents and reactants were of the best commercial grade available and were used without further purification unless noted. All H_2O used in the pH-stat kinetic study was doubly distilled and deionized. Ether was freshly distilled prior to use from sodium and benzophenone. Trichloroacetic acid-d_1, KD_2PO_4, and Tris-d_5 were made from trichloroacetic acid, KH_2PO_4, and Tris, respectively, and D_2O. Short-path, medium-pressure (5–20 psi) liquid chromatography was conducted with silica gel 60 PF254 (E. Merck No. 7747). Flash chromatography was performed with 40–63-μm (400–230 mesh) silica gel 60 (E. Merck No. 9387).[33] Thin-layer chromatographic analyses were run on precoated silica G microscope slides (2.5 × 10 cm; Analtech No. 01521) or on precoated silica GHLF microscope slides (10 × 20 cm; Analtech No. 21521).

Treatment of 6-Methoxyindene (17) with *N*-Bromosuccinimide and NaN_3. *N*-Bromosuccinimide (6.43 g, 36.1 mmol) was added in several portions to a stirred solution of indene **17** (3.77 g, 25.8 mmol) and NaN_3 (6.71 g, 103.3 mmol) in a 7:1 solution of 1,2-dimethoxyethane–H_2O (160 mL) at 0 °C. The *N*-bromosuccinimide was recrystallized from H_2O, and 1,2-dimethoxyethane was distilled over potassium prior to use. TLC analysis of the product mixture indicated that the reaction was not complete after 2 h at 0 °C. Accordingly, additional *N*-bromosuccinimide (6.43 g, 36.1 mmol) and NaN_3 (1.68 g, 25.8 mmol) were added in increments over the next 5 h. During the first 2 h the reaction was maintained at 0 °C, while the temperature during the last 3 h was 20 °C. Et_2O (225 mL) was then added, and the white solid that formed was filtered. The organic layer was separated, and the aqueous layer was extracted with ether (2 × 35 mL). The organic layers were combined, dried (Na_2SO_4), and evaporated in vacuo. TLC analysis of the residue after workup indicated the presence of **18** and an unidentified compound. The desired product was isolated by flash chromatography on SiO_2 using 5% ethyl acetate–hexane as the eluent.

The initial material eluting from the column was isolated as a yellow oil in 51% yield (3.53 g) and was identified as compound **18**: R_f 0.50 (5% ethyl acetate–hexane); IR (neat, NaCl) 3050, 2940, 2820, 2080, 1605, 1580, 1480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.20 (dd, J = 16.1, 6.3 Hz, $H_{3\alpha}$), 3.53 (dd, J = 16.1, 6.9 Hz, $H_{3\beta}$), 3.83 (s, OCH_3), 4.38–4.44 (m, H_2), 5.00 (d, J = 5.4 Hz, H_1), 6.90–6.97 (m, H_5, H_7), 7.17 (d, J = 8.1 Hz, H_4);[34] ^{13}C NMR (75 MHz, $CDCl_3$) 40.42 (t, J = 135.2 Hz, C_3), 51.32 (d, J = 157.6 Hz, C_2Br), 55.18 (q, J = 144.0 Hz, OCH_3), 73.04 (d, J = 151.5 Hz, C_1N_3), 109.05 (d, J = 159.8 Hz, C_5), 115.56 (d, J = 161.1 Hz, C_7), 125.27 (d, J = 161.1 Hz, C_4), 131.48 (s, C_{3a}), 139.15 (s, C_{7a}), 159.29 (s, C_6) ppm; M_r 267.00031 (calcd for $C_{10}H_{10}{}^{79}BrN_3O$, 267.00071).

Preparation of 6-Methoxyindano[1,2-*b*]aziridine (8). To a suspension of $LiAlH_4$ (51 mg, 1.3 mmol) in freshly distilled anhydrous Et_2O (15 mL) was added dropwise at 0 °C under N_2 a solution of **18** (200 mg, 0.8 mmol) in anhydrous Et_2O (5 mL). The suspension was stirred at 0 °C (45 min) and at room temperature (45 min). The reaction was then cooled to 0 °C with an ice–salt bath and then quenched by ice–H_2O (3 mL) and 0.1 N aqueous NaOH (2 mL). The white paste formed was filtered through Celite, and the ethereal layer was separated. The aqueous layer was saturated with NaCl and then extracted with Et_2O (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the Et_2O was concentrated (~1.5 mL) under high vacuum and then immediately dissolved in 1% triethylamine–ethyl acetate (1 mL) to avoid decomposition. Flash chromatography on a prewashed (1% triethylamine–ethyl acetate) SiO_2 column under N_2 using 1% triethylamine–ethyl acetate as the eluent gave **8** as a light yellow oil in 75% yield (90 mg): R_f 0.25 (10% ethyl acetate–hexane); R_f 0.35 (40% acetone–ether); R_f 0.75 (100% methanol); IR ($CHCl_3$) 3280, 3240, 2960, 2850, 1600, 1580, 1480 cm^{-1}; UV (CH_3CN) 284 (max), 290 (sh) nm; ^1H NMR (300 MHz, $CDCl_3$) δ 3.01–3.04 (br s, H_2, $H_{3\alpha}$, $H_{3\beta}$), 3.18–3.20 (br s, H_1), 3.68 (s, OCH_3), 6.70 (dd, J = 8.2, 2.5 Hz, H_5), 6.97 (d, J = 2.5 Hz, H_7), 7.08 (d, J = 8.2 Hz, H_4); ^{13}C NMR (75 MHz, $CDCl_3$) 34.46 (C_3), 36.52 (C_2), 39.78 (C_1), 55.13 (OCH_3), 109.99 (C_5), 112.55 (C_7), 126.70 (C_4), 132.65 (C_{3a}), 146.22 (C_{7a}), 158.22 (C_6) ppm; MS, m/e (relative intensity) 162 (18), 161 (73), 160 (100), 147 (16), 146 (78), 145 (17), 118 (33), 117 (60), 116 (18), 103 (20), 91 (22), 90 (10), 89 (16); M_r 161.08352 (calcd for $C_{10}H_{11}NO$, 161.08406). Compound **8** was stored in a 1% triethylamine–ethyl acetate solution at 5 °C.

Preparation of 6-Methoxy-1-aminoindan (33). To a suspension of $LiAlH_4$ (0.80 g, 21.0 mmol) in freshly distilled anhydrous Et_2O (110 mL) was added at 0 °C under N_2 a solution of **18** (3.13 g, 11.7 mmol) in anhydrous Et_2O (40 mL). The suspension was stirred at room temperature (3 h). The reaction was cooled to 0 °C and quenched by addition of ice–H_2O (30 mL). The white paste formed was filtered through Celite, and the ethereal layer was separated. The aqueous layer was saturated with NaCl and extracted with Et_2O (2 × 20 mL). The organic layers were combined, dried (Na_2SO_4), and evaporated to near dryness (1.5 mL). Flash chromatography on SiO_2 (25% chloroform–hexane) yielded **33** in 24% yield (0.45 g): mp 190–192 °C; R_f 0.15 (5% methanol–chloroform); IR (KBr) 3400, 2940, 1620, 1500 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 2.05–2.14 (m, $H_{2\beta}$), 2.56–2.66 (m, $H_{2\alpha}$), 2.85–2.95 (m, $H_{3\beta}$), 3.03–3.13 (m, $H_{3\alpha}$), 3.79 (s, OCH_3), 4.73 (dd, J = 7.8, 5.1 Hz, H_1), 6.91 (dd, J = 8.3, 2.3 Hz, H_5), 7.10 (d, J = 2.3 Hz, H_7), 7.22 (d, J = 8.3 Hz, H_4);[34] ^{13}C NMR (75 MHz, CD_3OD) 30.19 (C_2), 32.17 (C_3), 56.05 (OCH_3), 57.16 (C_1-NH_2), 110.47 (C_5), 117.17 (C_7), 126.98 (C_4), 130.23 (C_{3a}), 140.99 (C_{7a}), 160.90 (C_6) ppm; MS, m/e (relative intensity) 163 (32), 162 (79), 147 (38), 146 (100), 132 (27), 131 (29), 103 (26), 91 (27), 77 (27), 69 (15); M_r 163.10012 (calcd for $C_{10}H_{13}NO$, 163.09971).

Preparation of 6-Methoxy-*trans*-2-amino-1-indanol (35) and 6-Methoxy-*cis*-2-amino-1-indanol (36). To a stirred solution of **8** (0.10 g, 0.6 mmol) in H_2O (1 mL) was added aqueous 2.3 N $HClO_4$ (2 mL, 4.6 mmol) at 0 °C. The mixture was stirred at 0 °C (1 h) and then at room temperature (20 min). The reaction was made basic (pH 9) with aqueous dilute NH_4OH at 0 °C and then extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried (K_2CO_3), filtered, and evaporated to dryness to give a light red solid (79 mg, 71%). ^{13}C NMR and TLC analyses indicated the presence of compounds **35** and **36** in an approximate ratio of 1:4. Purification of the mixture was accomplished by flash chromatography (SiO_2, 100% CH_3OH). The minor product (**35**) obtained in 14% yield (16 mg) was identified as 6-methoxy-*trans*-2-amino-1-indanol: mp 121–123 °C; R_f 0.35 (100% methanol); IR (KBr) 3320 (br), 3030, 1620, 1500, 1390 cm^{-1}; UV (H_2O) 281 nm; ^1H NMR (300 MHz, CD_3OD) δ 2.53 (dd, J = 15.1, 8.5 Hz, $H_{3\beta}$), 3.09 (dd, J = 15.1, 7.5 Hz, $H_{3\alpha}$), 3.30–3.40 (m, H_2), 3.76 (s, OCH_3), 4.70 (d, J = 6.5 Hz, H_1), 6.77 (dd, J = 8.3, 2.5 Hz, H_5), 6.88 (d, J = 2.5 Hz, H_7), 7.06 (d, J = 8.3 Hz, H_4);[34] ^{13}C NMR (75 MHz, CD_3OD) 37.84 (C_3), 55.81 (OCH_3), 63.71 (C_2NH_2), 83.53 (C_1OH), 109.97 (C_5), 115.32 (C_7), 126.37 (C_4) ppm. The concentration of the sample did not allow the detection of the three quaternary aromatic carbon signals. MS, m/e (relative intensity) 179 (30), 160 (30), 150 (100), 149 (22), 146 (18), 134 (28), 121 (27), 119 (23), 91 (42), 77 (31); M_r 179.09420 (calcd for $C_{10}H_{13}NO_2$, 179.09462).

The second compound (**36**) that eluted from the column was obtained in 52% yield (58 mg) and was identified as 6-methoxy-*cis*-2-amino-1-indanol: mp 119–121 °C; R_f 0.30 (100% methanol); IR (KBr) 3340, 3280, 3120 (br), 2900, 1600, 1580, 1490, 1380 cm^{-1}; UV (H_2O) 281 nm; ^1H NMR (300 MHz, CD_3OD) δ 2.66 (dd, J = 15.2, 6.2 Hz, $H_{3\beta}$), 2.97 (dd, J = 15.2, 6.8 Hz, $H_{3\alpha}$), 3.40–3.50 (m, H_2), 3.76 (s, OCH_3), 4.79 (d, J = 5.3 Hz, H_1), 6.79 (dd, J = 8.3, 2.4 Hz, H_5), 6.94 (d, J = 2.4 Hz, H_7), 7.10 (d, J =

(33) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2926.

(34) The ^1H NMR assignment was supported by extensive ^1H–^1H decoupling experiments; see ref 1 for additional details.

8.3 Hz, H_4);[34] ^{13}C NMR (75 MHz, CD_3OD) 38.24 (C_3), 55.82 (OCH_3), 57.24 (C_2NH_2), 76.87 (C_1OH), 111.24 (C_5), 115.81 (C_7), 126.74 (C_4), 134.31 (C_{3a}), 145.87 (C_{7a}), 160.61 (C_6) ppm; MS, *m/e* (relative intensity) 179 (26), 160 (38), 150 (100), 149 (24), 146 (33), 134 (42), 121 (34), 119 (25), 91 (38), 77 (34); M_r 179.09504 (calcd for $C_{10}H_{13}NO_2$, 179.09462).

Treatment of 7-Methoxyindene (25) with *N*-Bromosuccinimide and NaN_3. Recrystallized *N*-bromosuccinimide (9.25 g, 51.9 mmol) was added in several portions (30 min) to a stirred solution of **25** (5.42 g, 37.1 mmol) and NaN_3 (9.65 g, 148.5 mmol) in a 7:1 mixture of distilled 1,2-dimethoxyethane–H_2O (260 mL) maintained at 0 °C. The reaction was stirred at 0 °C for 150 min and for an additional 20 min at room temperature. After workup using the procedure described for **18**, TLC analysis (10% ethyl acetate–hexane) of the crude product (9.16 g) indicated the presence of three compounds: **26** (R_f 0.75), **27** (R_f 0.60), and **28** (R_f 0.10) in an approximate ratio of 3:1:2, respectively.

Recrystallization of the crude mixture from ether–hexane gave **28** in 30% yield (2.65 g) as cream color needles. Compound **28** was identified as 7-methoxy-2-bromo-1-indanol: mp 133–135 °C; R_f 0.10 (10% ethyl acetate–hexane); R_f 0.45 (30% ethyl acetate–hexane); R_f 0.40 (100% chloroform); IR (KBr) 3160, 2980, 2940, 2820, 1605, 1590, 1480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.21 (dd, J = 16.8, 5.6 Hz, $H_{3\alpha}$), 3.67 (dd, J = 16.8, 7.1 Hz, $H_{3\beta}$), 3.87 (s, OCH_3), 4.37–4.43 (m, H_2), 5.54 (d, J = 3.8 Hz, H_1), 6.59 (d, J = 8.2 Hz, H_6), 6.84 (d, J = 7.5 Hz, H_4), 7.28 (br t, J = 7.8 Hz, H_5); ^{13}C NMR (75 MHz, $CDCl_3$) 41.35 (C_3), 52.97 (C_2Br), 55.27 (OCH_3), 82.07 (C_1OH), 108.99 (C_6), 117.14 (C_4), 129.01 (C_{7a}), 130.84 (C_5), 142.18 (C_{3a}), 156.36 (C_7) ppm; MS, *m/e* (relative intensity) 244 (14), 242 (14), 163 (100), 146 (27), 131 (23), 115 (27), 103 (43), 91 (29), 77 (22); M_r 241.99511 (calcd for $C_{10}H_{11}{}^{79}BrO_2$, 241.99423).

The ether–hexane filtrate was purified by flash chromatography on SiO_2 using 5% ethyl acetate–hexane as the eluent. The first product **26** that was collected from the column was obtained as a yellow oil in 40% yield (4.00 g): R_f 0.75 (10% ethyl acetate–hexane); IR (neat, NaCl) 3010, 2950, 2840, 2100, 1600, 1585, 1480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.26 (dd, J = 17.5, 2.5 Hz, $H_{3\alpha}$), 3.73 (dd, J = 17.5, 6.2 Hz, $H_{3\beta}$), 3.89 (s, OCH_3), 4.45–4.48 (m, H_2), 5.32 (d, J = 2.0 Hz, H_1), 6.84 (d, J = 8.2 Hz, H_6), 6.92 (d, J = 7.5 Hz, H_4), 7.36 (br t, J = 7.9 Hz, H_5);[34] ^{13}C NMR (75 MHz, $CDCl_3$) 42.07 (dddd, J = 138.1, 130.2, 3.2, 2.9 Hz, C_3), 51.50 (ddd, J = 160.4, 6.2, 4.7 Hz, C_2Br), 55.29 (q, J = 144.6 Hz, OCH_3), 71.72 (d of m, J = 156.3 Hz, C_1N_3), 109.21 (dd, J = 158.8, 8.0 Hz, C_6), 117.20 (dd, J = 161.1, 7.8 Hz, C_4), 125.10 (s, C_{7a}), 131.52 (d, J = 159.2 Hz, C_5), 142.87 (s, C_{3a}), 157.08 (s, C_7) ppm. Selective irradiation of the signal at δ 5.32 in the ^1H NMR spectrum collapsed the multiplet at 71.72 ppm in the ^{13}C NMR coupled spectrum to a broad singlet. Selective irradiation of the signal at δ 4.45–4.48 in the ^1H NMR spectrum collapsed the multiplet at 51.50 in the ^{13}C NMR coupled spectrum to a broad singlet. MS, *m/e* (relative intensity) 227 (37), 225 (37), 147 (13), 146 (100), 117 (40), 103 (50), 89 (50); M_r 267.00113 (calcd for $C_{10}H_{10}{}^{79}BrN_3O$, 267.00071).

The final adduct **27** that eluted from the column was obtained in 15% yield (1.50 g) as a yellow oil: R_f 0.60 (10% ethyl acetate–hexane); IR (neat, NaCl) 3005, 2950, 2840, 2100, 1590, 1470 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.31 (d, J = 8.3 Hz, $H_{3\alpha}$, $H_{3\beta}$), 3.89 (s, OCH_3), 4.49–4.57 (m, H_2), 5.04 (d, J = 5.7 Hz, H_1), 6.38 (d, J = 8.0 Hz, H_6), 6.85 (d, J = 7.3 Hz, H_4), 7.30 (br t, J = 7.6 Hz, H_5);[34] ^{13}C NMR (75 MHz, $CDCl_3$) 41.10 (C_3), 49.37 (C_1Br), 55.34 (OCH_3), 64.83 (C_2N_3), 109.23 (C_6), 116.50 (C_4), 126.13 (C_{7a}), 131.37 (C_5), 143.14 (C_{3a}), 156.30 (C_7) ppm; MS, *m/e* (relative intensity) 269 (5), 227 (58), 225 (60), 146 (100), 145 (47), 131 (27), 117 (45), 103 (40); M_r 267.00040 (calcd for $C_{10}H_{13}{}^{79}BrN_3O$, 267.00071).

Preparation of 7-Methoxyindano[1,2-*b*]aziridine (9). To a suspension of $LiAlH(Ot\text{-}Bu)_3$ (0.83 g, 3.3 mmol) in distilled anhydrous Et_2O (10 mL) was added dropwise at 0 °C (internal temperature) under N_2 a solution of **26** (0.35 g, 1.3 mmol) in anhydrous Et_2O (10 mL). The mixture was stirred at 20 °C (internal temperature) for 1 h and then at 30 °C (internal temperature) for an additional 24 h. The reaction was cooled to 0 °C and was quenched by the alternative addition of ice–H_2O (5 mL) and aqueous 5% NaOH (5 mL). The internal temperature was kept below 3 °C throughout this procedure. The white paste that formed was filtered through Celite previously washed with aqueous 0.001 N NaOH (2 × 10 mL). The ethereal layer was separated, and the aqueous layer was saturated with NaCl and then extracted with Et_2O (2 × 10 mL). The combined ethereal layers were dried (K_2CO_3), filtered, and evaporated to near dryness (3 mL). The ether component of the solution was then progressively replaced by a 1% triethylamine–acetonitrile solution by using reduced pressure to remove the ether, and the solution was then concentrated to 1.5 mL. Flash chromatography on SiO_2 (prewashed with 1% triethylamine–acetonitrile) using 1% triethylamine–acetonitrile as the eluent under N_2 gave **9** (estimated amount 2 mg, approximately 1% yield). Removal of the chromatographic solvents was facilitated by the addition of pentane to the fractions containing **9** (13% acetonitrile–pentane azeotrope, bp 58 °C, 124 Torr; 36.8% acetonitrile–triethylamine azeotrope, bp 29 °C, 152 Torr).[35] Compound **9** was never concentrated to dryness to avoid decomposition of this adduct and was used within hours after purification: R_f 0.25 (10% ethyl acetate–hexane); R_f 0.35 (40% acetone–ether); R_f 0.75 (100% CH_3OH); ^1H NMR (300 MHz, CD_3CN) δ 2.95–2.98 (br s, H_2, $H_{3\alpha}$, $H_{3\beta}$), 3.24–3.28 (br s, H_1), 3.79 (s, OCH_3), 6.71 (d, J = 8.2 Hz, H_6), 6.75 (d, J = 7.6 Hz, H_4), 7.09 (br t, J = 8.1 Hz, H_5); ^{13}C NMR (75 MHz, $CDCl_3$) 36.59 (C_3), 36.86 (C_2), 37.85 (C_1), 56.55 (OCH_3), 109.91 (C_6), 119.97 (C_4), 130.02 (C_5) ppm. The concentration of the sample did not allow the detection of the three quaternary aromatic carbon signals. MS, *m/e* (relative intensity) 162 (41), 161 (100), 147 (14), 146 (14), 145 (26), 133 (7), 117 (10), 103 (7), 91 (7), 90 (7), 89 (7), 77 (9).

Preparation of 7-Methoxy-*trans*-2-amino-1-indanol (37) and 7-Methoxy-*cis*-2-amino-1-indanol (38). To a stirred aqueous 2.3 N solution of $HClO_4$ (2 mL, 4.6 mmol) at 0 °C was added a solution of **9** (1 mg, 0.006 mmol) in CH_3CN (0.5 mL). The solution turned instantly to bright yellow. The reaction was stirred at 0 °C (40 min) and then quenched at 0 °C with cold aqueous concentrated NH_4OH to pH 8. The solution was saturated with NaCl and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined and then washed with saturated aqueous brine (2 × 5 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo. TLC analysis (100% methanol) of the residue showed the presence of two compounds, **37** (R_f 0.30) and **38** (R_f 0.25), in an approximate ratio of 1:4, respectively. These two adducts were separated by flash chromatography on SiO_2 (100% CH_3OH). The first compound that eluted from the column was obtained in approximately 20% yield (0.2 mg) and was identified as 7-methoxy-*trans*-2-amino-1-indanol (**37**): mp 123–125 °C; R_f 0.30 (100% CH_3OH); FT-IR (CD_3OD) 3353 (br), 2927, 1598, 1483, 1442, 1384, 1270 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 2.50 (dd, J = 16.1, 4.1 Hz, $H_{3\beta}$), 3.27–3.35 (m, $H_{3\alpha}$), 3.43–3.49 (m, H_2), 3.79 (s, OCH_3), 4.88 (d, J = 3.1 Hz, H_1), 6.74 (d, J = 8.3 Hz, H_6), 6.77 (d, J = 7.7 Hz, H_4), 7.19 (br t, J = 7.8 Hz, H_5); ^{13}C NMR (75 MHz, CD_3OD) 39.57 (C_3), 55.35 (OCH_3), 61.35 (C_2NH_2), 81.61 (C_1OH), 109.61 (C_6), 118.16 (C_4), 131.19 (C_5) ppm. The concentration of the sample did not allow the detection of the remaining three quaternary aromatic carbon signals. MS, *m/e* (relative intensity) 179 (25), 161 (63), 150 (100), 146 (52), 133 (47), 118 (34), 103 (24), 91 (42), 77 (21); M_r 179.09386 (calcd for $C_{10}H_{13}NO_2$, 179.09462).

The second compound was isolated in approximately 70% yield (0.7 mg) and was identified as 7-methoxy-*cis*-2-amino-1-indanol (**38**): mp 120–122 °C; R_f 0.25 (100% methanol); IR (KBr) 3420 (br), 2960, 2910, 2840, 1605, 1585, 1480, 1450, 1265 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 2.74 (dd, J = 15.4, 9.2 Hz, $H_{3\beta}$), 3.00 (dd, J = 15.4, 7.6 Hz, $H_{3\alpha}$), 3.38–3.45 (m, H_2), 3.84 (s, OCH_3), 4.92 (d, J = 5.0 Hz, H_1), 6.77–6.81 (m, H_6, H_4), 7.22 (t, J = 7.9 Hz, H_5);[34] ^{13}C NMR (75 MHz, CD_3OD) 39.60 (C_3), 56.61 (OCH_3), 57.70 (C_2NH_2), 74.04 (C_1OH), 110.75 (C_6), 116.99 (C_4), 130.41 (C_5) ppm. The concentration of the sample did not allow the detection of the remaining three quaternary aromatic carbon signals. MS, *m/e* (relative intensity) 179 (29), 161 (85), 150 (85), 146 (100), 133 (45), 118 (45), 103 (36), 91 (47); M_r 179.09437 (calcd for $C_{10}H_{13}NO_2$, 179.09462).

Hydrolysis of 8. a. ^1H NMR Kinetic Experiments. Kinetic data were obtained on a Nicolet NT-300 WB ^1H NMR spectrometer. In a typical experiment, an ice-chilled solution of **8** (~0.6 M) in CD_3CN (0.1 mL) was syringed into a 5-mm NMR

(35) Rappoport, Z. *Handbook of Tables for Organic Compounds Identification*, 3rd ed.; CRC: Cleveland, OH, 1967.

tube containing the buffered D_2O solution (0.5 mL). The reaction mixture was then immediately placed into the NMR (300.1 MHz) probe, which had been previously equilibrated at 25 ± 1 °C. The NMR kinetic experiment was then initiated by collecting every minute 1 data-block of 12 acquisitions. Twenty data blocks were recorded and then processed. The hydrolysis was followed for 2 half-lives by monitoring the appearance of the C-1 methine hydrogens for **43** (**35**) and **44** (**36**) as a function of time. The percentage of conversion to products was determined by comparing the H area for the C-1 methine hydrogen atom for **43** and **44** with the combined aromatic hydrogen atoms for **8**, **43** (**35**) and **44** (**36**). A minimum of five points (plus time 0) spread out over at least 2 half-lives were obtained. Standard data plots yielded linear slopes through this period from which psuedo-first-order rate constants were calculated. The pD of the solution was determined at the conclusion of the reaction from the observed pH meter reading by using the relationship[30] pD = pH meter reading + 0.4. Observed first-order rate constants (reciprocal seconds) and half-lives (minutes) for the hydrolysis of **8** obtained by this procedure were as follows (pD, k_{obsd} (10^4), $t_{1/2}$): 1.8, 42, 2.8; 5.1, 55, 2.2; 6.6, 32, 3.6; 7.8, 9, 12.2; 8.3, 1, 128.4.

b. pH-stat Kinetic Experiments. The reaction was carried out in a Radiometer titration vessel (20 mL) maintained at 25 ± 1 °C with an external thermostated bath. The cell was mounted by a four-hole stopper which held the electrode, the titrant delivery tube, and the inert gas (N_2) tube. The remaining entry hole was used to inject into the reaction the starting aziridine as well as concentrated HCl. Deionized H_2O (10 mL) was placed in the glass cell and was degassed by bubbling N_2 through the solution (20 min). The H_2O was kept under a stream of N_2 after this period of time. The ABU12 autoburet was charged with aqueous HCl titrant (1.0×10^{-3} or 5×10^{-3} M), and the speed of addition was set to deliver either 0.5 or 1.0 mL of titrant per minute. Approximately 1 mL of a stock solution of 6-methoxyindano[1,2-*b*]aziridine (**8**) in CH_3CN (~25 mM) was then added to the cell, leading to an increase in the initial pH of the degassed water from approximately 6.5 to 9.0. The pH of the reaction was then rapidly readjusted to the desired pH value by injecting with a syringe a known amount of aqueous HCl into the reaction vessel. The titrator was then set to maintain this pH value, and the instrument was started. The volume of titrant added was recorded as a function of time. The initial time of the kinetic experiment was taken as the time the pH of the solution reached the preselected pH value. The reaction was carried out for at least 4 half-lives, and the total volume of titrant added by the autoburet was recorded. Standard data plots yielded nicely linear slopes through this period from which psuedo-first-order rate constants were calculated. Observed first-order rate constants (reciprocal seconds) and half-lives (minutes) for the hydrolysis of **8** obtained by this procedure were as follows (pH, k_{obsd} (10^4), $t_{1/2}$): 5.45, 96.2, 1.2; 6.00, 109.4, 1.0; 6.50, 50.6, 2.3; 7.32, 16.7, 6.9; 7.82, 6.1, 19.0; 8.19, 2.6, 44.4; 8.38, 1.7, 68.0.

At the conclusion of each hydrolysis, the reaction was made basic (pH 9) with an aqueous NaOH (10^{-3} N) solution. The reaction solution was then saturated with NaCl and extracted with CH_2Cl_2 (2 × 5 mL). The organic layers were combined, washed with saturated aqueous brine (5 mL), dried (Na_2SO_4), and filtered. TLC analysis (100% CH_3OH) of the solution showed the presence of two compounds at R_f 0.35 and 0.30 in an approximate ratio of 1:2, respectively, at all the pH values examined. The R_f values corresponded to **35** and **36**, respectively. The CH_2Cl_2 layers from several kinetic experiments were pooled, and the solvent was removed in vacuo. The ^1H NMR spectrum of the residue revealed the presence of both 6-methoxy-*trans*-2-amino-1-indanol (**35**) and 6-methoxy-*cis*-2-amino-1-indanol (**36**) in an approximate ratio of 1:2, respectively.

Hydrolysis of 9. pH-stat Kinetic Experiments. The general experimental protocol utilized for the hydrolysis of **8** was modified in this study. The initial deionized H_2O solvent was replaced by an aqueous 10^{-4} N NaOH solution, and the solution was degassed (20 min) at the desired temperature. One milliliter of a stock solution of **9** in acetonitrile (~1 mM) was then added to the thermostated cell. The titration instrument was started, and the volume of acid added to maintain the pH at the preselected value (8.88) was recorded as a function of time. The initial time of the kinetic study was taken as the time the pH of the reaction reached 8.88. The reaction was carried out for at least 8 half-lives, and the total volume of titrant added was recorded. Observed first-order rate constants (reciprocal seconds) and half-lives (minutes) for the hydrolysis of **9** obtained by this procedure were as follows (temperature (°C), k_{obsd} (10^4), $t_{1/2}$): 25, 136, 0.9; 14, 44, 2.6; 10, 34, 3.4.

At the end of each hydrolysis, the reaction was made basic to pH 10 with an aqueous NaOH (10^{-3} N) solution. The reaction was then worked-up by using a procedure identical with that described in the hydrolysis of aziridine **8**. TLC analysis (100% CH_3OH) of the CH_2Cl_2 solution revealed the presence of two compounds at R_f 0.30 and 0.25 in an approximate ratio of 1:2, respectively, at all the pH values examined. The R_f values corresponded to **37** and **38**, respectively. The CH_2Cl_2 solutions obtained after workup of each hydrolysis were pooled, and the solvent was evaporated in vacuo. The residue was then purified by flash chromatography (SiO_2, 100% CH_3OH). ^1H NMR spectroscopy revealed the presence of 7-methoxy-*trans*-2-amino-1-indanol (**37**) and 7-methoxy-*cis*-2-amino-1-indanol (**38**) in an approximate ratio of 1:2, respectively.

Acknowledgment. We thank the National Institutes of Health (Grant No. CA 29756) and the Robert A. Welch Foundation for their generous support of this research.