(75 MHz, $CDCl_3$) δ 150.7, 138.2, 133.8, 130.9, 129.0, 127.8, 124.2, 106.2, 58.9 (two coincident peaks), 43.1, 36.7, 31.6, 29.6, 27.8, 26.0, 22.6, 20.7, 17.9, 14.1, 12.6, -3.4, -3.7; MS (CI, isobutane) *m/e* 498 (MH^+, base peak).

Acknowledgment. We gratefully acknowledge the Duke University Research Council for support of this work. L.W.D. thanks Duke University for a Charles R. Hauser Fellowship (1990-1991). We thank Dr. Larry Overman of the University of California, Irvine, for helpful discussions on the oxidation of intermediate 7 and Dr. Paul Grieco of Indiana University and Dr. David Evans of Harvard University for helpful discussions on the reduction of octahydroquinolines. We thank Dr. Tom Spande, Dr. John Daly, and Dr. Herman Yeh of the Laboratory of BioOrganic Chemistry, NIH, for helpful discussions, analysis, and acquiring spectra of 2-*epi*-**195A** and *N*-Me-2-*epi*-**195A**. High-field NMR spectra were recorded at the Duke University Spectroscopy Center, funded by NSF Grant DMB8501010, NIH Grant RR62780, and NC Biotechnology Grant 86U02151.

A Novel Stereospecific Rearrangement of 3-Substituted B-Homo 5-Azasteroids to Their A-Nor Analogues. Preparation, Stereochemistry, and Conformational Studies

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The novel 3α- and 3β-hydroxy-*B*-homo-5-azasteroid lactams **4** and **5** were prepared from testosterone. When the hydroxyl group in these compounds is converted into a leaving group, rearrangement to the corresponding A-nor azasteroids occurs under a variety of conditions, along with competing substitution with inversion of configuration at C-3. The rearrangements proceed with complete stereospecificity and are faster and more efficient in the 3α-series. The observed stereochemistry, as well as the results of molecular modeling, low-temperature NMR, and X-ray crystallographic studies support a mechanism involving neighboring-group participation by the nitrogen atom in the departure of the nucleofuge from C-3 via the formation of aziridinium ion intermediates. Compounds in the 3α-series require prior ring-flipping to the A-boat conformation, while those in the 3β-series react through the corresponding A-chairs. The differences in the free energies of the A-boat and A-chair forms are greater in the 3β-compounds (1.6-3.4 kcal/mol) than in the corresponding 3α-isomers (0.1-1.3 kcal/mol). The 3α-chloro derivative **19** exists mainly as the A-chair in solution (ΔG = 0.3 kcal/mole; ΔG^* = 12.2 kcal/mol), but crystallizes in the A-boat conformation. Molecular modeling studies of several 3-substituted derivatives and X-ray investigations of **19** and its 3β-isomer **20** also reveal separate flip forms of the B-rings associated with the A-chair and A-boat conformations in each case. Relief of steric hindrance between one of the hydrogen atoms at C-19 and the β-hydrogen at C-7 (this H-H contact is only 1.98 Å in the crystal structure of **19**) in the A-boat conformations of the 3α-series enhances anchimeric assistance to the departure of the leaving group and facilitates the rearrangements of these compounds relative to their 3β-counterparts.

Azasteroids display diverse types of biological activity,[2] and consequently their preparation and further transformations are of importance.[3] Our work with azasteroids[4] has been directed toward the design and synthesis of novel analogues where the nitrogen atom is part of a latent or existing reactive functionality that can be used to form covalent bonds with complementary groups within the active sites of receptor proteins or enzymes involved in steroid biosynthesis.

Such compounds have possible uses as affinity labels, enzyme inhibitors, and anticancer agents. In particular, we wished to determine whether neighboring group participation by a nitrogen atom placed at the 5-position would affect the behavior of nucleofugal substituents attached at C-3. By analogy, the alkylating properties of

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(2) The following are examples of azasteroids with biological activity. 5α-Reductase inhibitors: (a) Rasmusson, G. H.; Reynolds, G. F.; Steinberg, N. G.; Walton, E.; Patel, G. F.; Liang, T.; Cascieri, M. A.; Cheung, A. H.; Brooks, J. R.; Berman, C. *J. Med. Chem.* **1986**, *29*, 2298. (b) Rasmusson, G. H.; Reynolds, G. F.; Utne, T.; Jobson, R. B.; Primka, R. L.; Berman, C.; Brooks, J. R. *J. Med. Chem.* **1984**, *27*, 1690. Inhibitors of 3β-hydroxy-Δ⁵-steroid dehydrogenase/3-keto-Δ⁵-steroid isomerase: (c) Brandt, M.; Levy, M. A. *Biochemistry* **1989**, *28*, 140. Antibiotic 25822 B: (d) Dolle, R. E.; Allaudeen, H. S.; Kruse, L. I. *J. Med. Chem.* **1990**, *33*, 877. (e) Barton, D. H. R.; Lusinchi, X.; Menéndez, A. M.; Milliet, P. *Tetrahedron* **1983**, *39*, 2201. (f) Chamberlin, J. W.; Chaney, M. O.; Chen, S.; Demarco, P. V.; Jones, N. D.; Occolowitz, J. L. *J. Antibiotics* **1974**, *27*, 992. (g) Gordee, R. S.; Butler, T. F. *J. Antibiot.* **1975**, *28*, 112. Neuromuscular blocking agents: (h) Singh, H.; Bhardwaj, T. R.; Ahuja, N. K.; Paul, D. *J. Chem. Soc., Perkin Trans. 1* **1979**, 305. (i) Gandiha, A.; Marshall, I. G.; Paul, D.; Singh, H. *J. Pharm. Pharmacol.* **1974**, *26*, 871. Antimicrobial agents: (j) Chesnut, R. W.; Durham, N. N.; Brown, R. A.; Mawdsley, E. A.; Berlin, K. D. *Steroids* **1976**, *27*, 525. (k) Solomons, W. E.; Doorenbos, N. J. *J. Pharm. Sci.* **1974**, *63*, 19. (l) Doorenbos, N. J.; Solomons, W. E. *J. Pharm. Sci.* **1973**, *62*, 638. (m) Doorenbos, N. J.; Vaidya, S. S.; Havranek, R. E. *Chem. Ind.* **1967**, 704. Hypocholesterolemics: (n) Counsell, R. E.; Klimstra, P. D.; Ranney, R. E.; Cook, D. L. *J. Med. Pharm. Chem.* **1962**, *5*, 720. (o) Counsell, R. E.; Klimstra, P. D.; Nysted, L. N.; Ranney, R. E. *J. Med. Chem.* **1965**, *8*, 45.

(3) (a) Huisman, H. O. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 450. (b) Huisman, H. O. In *Steroids*. Johns, W. F., Ed.; International Review of Science, Organic Chemistry Series 1, Butterworths: London, 1973; Vol. 8, Chapter 9. (c) Huisman, H. O.; Speckamp, W. N. *Ibid.* Series 2, 1976; Vol. 8, Chapter 8.

(4) (a) Back, T. G.; Chau, J. H.-L.; Dyck, B. P.; Gladstone, P. L. *Can. J. Chem.* **1991**, *69*, 1482. (b) Back, T. G.; Lai, E. K.-Y.; Morzycki, J. W. *Heterocycles* **1991**, *32*, 481. (c) Back, T. G.; Brunner, K. *J. Org. Chem.* **1989**, *54*, 1904. (d) Back, T. G.; Brunner, K.; Codding, P. W.; Roszak, A. W. *Heterocycl.* **1989**, *28*, 219. (e) Back, T. G.; Ibrahim, N.; McPhee, D. J. *J. Org. Chem.* **1982**, *47*, 3283. (f) Back, T. G. *J. Org. Chem.* **1981**, *46*, 1442.

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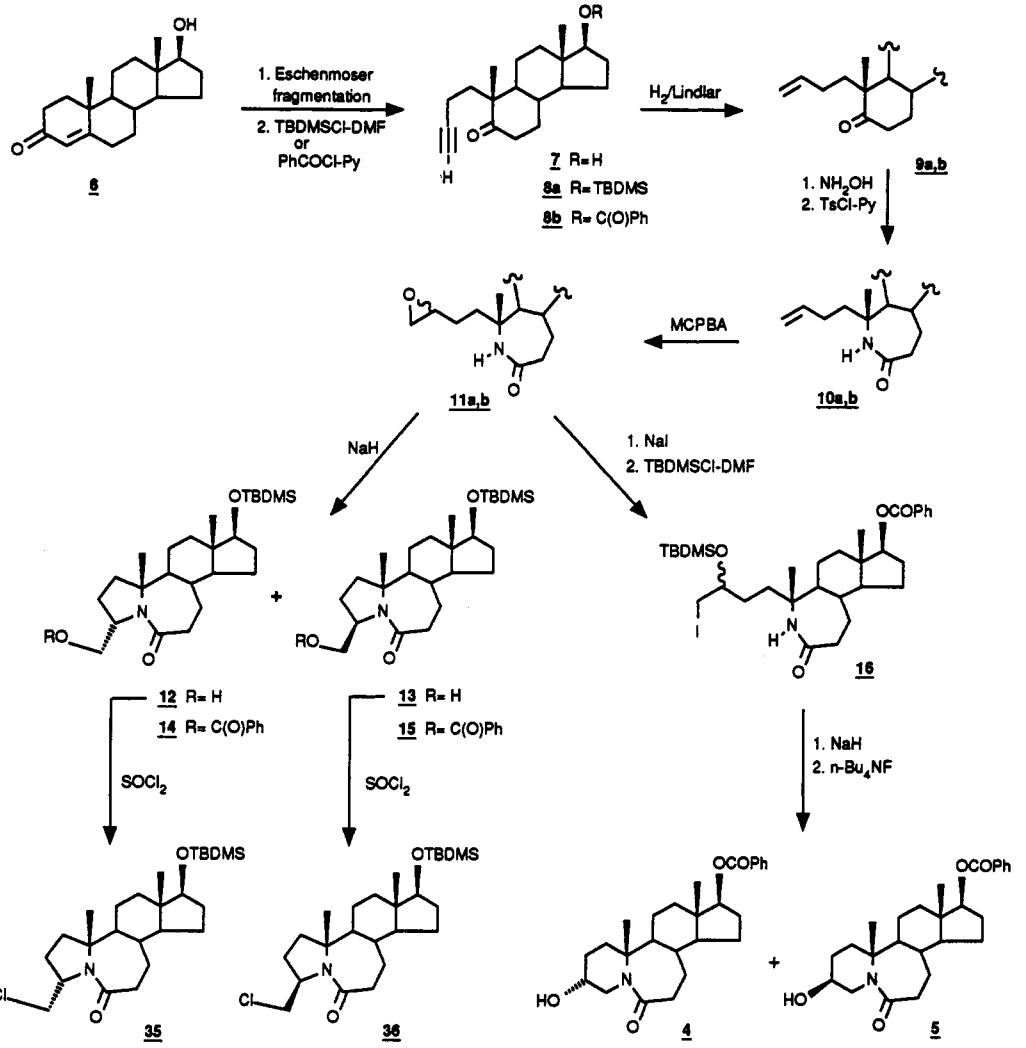
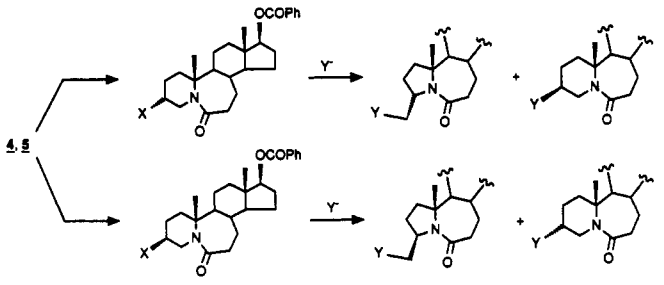
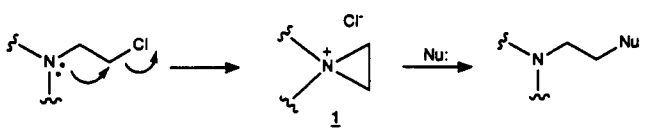
Scheme I



Scheme II

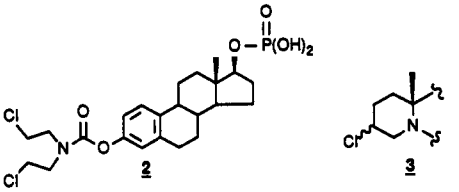


nitrogen mustards [bis(β-chloroethyl)amines] and half-mustards [(β-chloroethyl)amines] are attributed to anchimeric assistance to chloride departure by the nitrogen atom, resulting in the formation of electrophilic aziridinium ion intermediates **1** that react further with available nucleophiles[5] (eq 1).



(1)

A number of steroid derivatives containing pendant nitrogen mustard side chains have been reported to date,[6] and several underwent clinical trials for the treatment of breast and prostate cancers [e.g., Estracyt (**2**)].[6a] However,

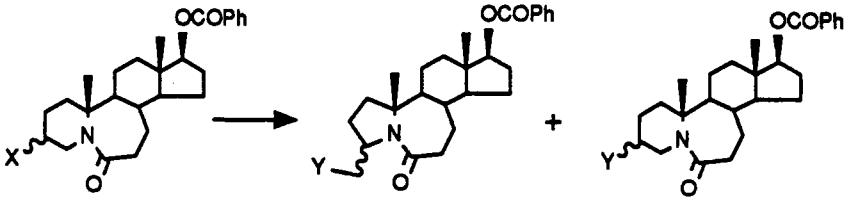


to our knowledge, there are no existing examples having nuclear (e.g. **3**), rather than extranuclear, (β-chloroethyl)amino groups.[7] We now report the preparation of

(5) Capon, B.; McManus, S. P. *Neighbouring Group Participation*; Plenum Press: New York, 1976; Vol. 1, Chapter 6.

(6) Estracyt: (a) Jönsson, G.; Olsson, A. M.; Luttrop, W.; Cekan, Z.; Purvis, K.; Diczfalusy, E. In *Vitamins and Hormones*; Munson, P. L., Diczfalusy, E., Glover, J., Olson, R. E., Eds.; Academic Press: New York, 1975; Vol. 33, p 351. (b) Leclercq, G.; Devleeschouwer, N.; Heuson, J. C. *J. Steroid Biochem.* **1983**, *19*, 75. For examples of other steroidal nitrogen mustards, see: (c) Leclercq, G.; Deboel, M.-C.; Heuson, J.-C. *Int. J. Cancer* **1976**, *18*, 750. (d) Dalmases, P.; Gomez-Belinchon, J. I.; Bonet, J.-J.; Giner-Sorolla, A.; Schmid, F. A. *Eur. J. Med. Chem. Chim. Ther.* **1983**, *18*, 541. (e) Catsoulacos, P.; Camoutsis, C.; Wampler, G. L. *Oncology* **1982**, *39*, 59. (f) Catsoulacos, P.; Politis, D.; Boutis, L.; Papageorgiou, A. *Eur. J. Med. Chem. Chim. Ther.* **1980**, *15*, 473. (g) Carroll, F. I.; Philip, A.; Blackwell, J. T.; Taylor, D. J.; Wall, M. E. *J. Med. Chem.* **1972**, *15*, 1158. (h) Nogrady, T.; Vagi, K. M.; Adamkiewicz, V. W. *Can. J. Chem.* **1962**, *40*, 2126.

Table I. Rearrangement of



starting material	conditns	time (h)	rearrangement product (yield, %)	substitution product (yield, %)
4; X = α-OH	$SOCl_2$, CH_2Cl_2, rt	4	21; Y = α-Cl (72)	
5; X = β-OH	$SOCl_2$, CH_2Cl_2, rt	60	22; Y = β-Cl (63)	19; Y = α-Cl (14)
17; X = α-OTs	LiCl, $Me_2C{=}O$, t-BuOH, Δ	8	21; Y = α-Cl (67)	20; Y = β-Cl (22)
18; X = β-OTs	LiCl, $Me_2C{=}O$, t-BuOH, Δ	48	22; Y = β-Cl (trace)	19; Y = α-Cl (81)
4; X = α-OH	Ph_3P, CCl_4, CH_2Cl_2, rt	16	21; Y = α-Cl (13)	20; Y = β-Cl (65)
5; X = β-OH	Ph_3P, CCl_4, CH_2Cl_2, rt	48		19; Y = α-Cl (88)
19; X = α-Cl	$AgNO_3$ (0.1 M), H_2O, THF, Δ	24	23; Y = α-OH (81)	
20; X = β-Cl	$AgNO_3$ (0.1 M), H_2O, THF, Δ	168	24; Y = β-OH (44)	

several 5-azasteroids containing leaving groups in the 3α- and 3β-positions. In addition to the expected nucleophilic substitution reactions, these compounds undergo novel, stereospecific rearrangements to ring-contracted A-nor products under a variety of conditions. We present evidence supporting neighboring-group participation by the nitrogen atom in the latter processes as well as a consideration of the attendant stereoelectronic and conformational factors.[8,9]

Results and Discussion

Preparation of B-Homo and A-Nor-B-homo 5-Azasteroids. The 3α- and 3β-hydroxy-*B*-homo-5-azasteroid lactams **4** and **5** were selected as key intermediates because of their accessibility via Scheme I and the facile conversion of their hydroxyl substituents into various 3α- and 3β-nucleofuges. Thus, while the preparation of 5-azasteroids with normal B-rings requires the degradation of C-5 in a carbocyclic precursor,[10] the expanded B-rings in **4** and **5** are easily obtained by means of highly regioselective Beckmann rearrangements of ketones **9a** and **9b** (the **a** and **b** series refer to 17-*tert*-butyldimethylsilyl ether and 17-benzoate derivatives, respectively, throughout). Moreover, the flexibility of the B-ring ensures that the system can adopt conformations that provide the opportunity for neighboring-group participation by the lactam nitrogen. Finally, lactams **4** and **5** provide the opportunity for reduction to the corresponding tertiary amine derivatives to provide a more reactive class of alkylating agents, where the absence of the delocalizing lactam carbonyl group should render the nitrogen lone pair more readily available for attack at C-3. The properties of the amine analogues will be reported separately.

The preparation of **4** and **5** is outlined in Scheme I. The Eschenmoser fragmentation of testosterone (**6**) to **7**,[11] followed by protection of the C-17 hydroxyl group, partial hydrogenation of the triple bond, Beckmann rearrangement, and epoxidation afforded epoxides **11a** and **11b** as mixtures containing approximately equal amounts of the two possible diastereomers. Direct base-promoted cyclization of **11a** resulted exclusively in 5-exo closure[12] to the A-nor alcohols **12** and **13**, which were easily separated as their benzoates **14** and **15**, respectively. The stereochemistry of these compounds was assigned on the basis of an observed NOE effect between the C-19 angular methyl group and the exocyclic 3-methylene protons of the 3β-benzoate **15**. No NOE effect was observed for the corresponding 3α-isomer **14**. The free alcohols **12** and **13** were regenerated by saponification of the separated benzoates. The 3-(hydroxymethyl)-A-nor structures of **12** and **13** were confirmed by their oxidation with pyridinium dichromate in dichloromethane to afford aldehyde products,[13] instead of ketones. The required 6-endo compounds **4** and **5** were obtained from epoxide **11b** via the iodohydrin silyl ether **16**. Stereochemical assignments were made for **4** and **5** and their derivatives on the basis of their ^1H NMR spectra, where compounds in the 3α-series showed signals for the C-3 proton at lower field and with smaller couplings than in the 3β-series.[14] Moreover, the assigned structures of the corresponding 3α- and 3β-chloro analogues **19** and **20**, as well as those of their A-nor analogues, were confirmed by X-ray crystallography (vide infra).

Rearrangements of 3-Substituted B-Homo 5-Azasteroids. When the hydroxyl functions of azasteroids **4** and **5** were converted into leaving groups, the resulting products underwent highly stereospecific rearrangements

(7) A major obstacle to clinical applications of extranuclear nitrogen mustards stems from their low binding affinities for their receptors (see ref 6c). Presumably, the perturbation to the normal steroid structure by the unnatural pendant group impedes recognition by the active site, thereby preventing the selective uptake of the alkylating agent by cells rich in steroid receptors. The use of nuclear alkylating agents that more closely resemble natural steroid hormones could result in improved recognition. While half-mustards such as those considered here could not cross-link DNA after translocation of the steroid–receptor complex into the cell nucleus, they could alkylate nucleophilic groups within the receptor itself, thereby acting as affinity labels or as antagonists of natural sex hormones, with potential medicinal applications.

(8) Preliminary communication: Back, T. G.; Chau, J. H.-L.; Morzycki, J. W. *Tetrahedron Lett.* **1991**, *32*, 6517.

(9) For a review of neighboring group effects of amides and their conjugate bases, see: (a) Shafer, J. A. In *The Chemistry of Amides*; Zabicky, J., Ed.; J. Wiley: New York, 1970; Chapter 12, pp 704–721. (b) Challis, B. C.; Challis, J. A. *Ibid.* Chapter 13, pp 742–752.

(10) For examples of true 5-azasteroids, see: (a) Rodewald, W. J.; Achmatowicz, B. *Tetrahedron* **1971**, *27*, 5467. (b) Rodewald, W. J.; Jaszczyński, J. R. *Tetrahedron Lett.* **1976**, 2977.

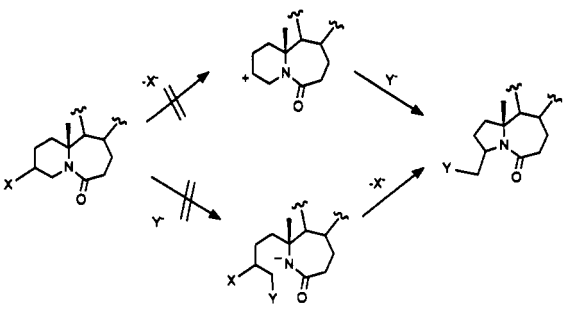
(11) Boar, R. B.; Jones, S. L.; Patel, A. C. *J. Chem. Soc., Perkin Trans. 1* **1982**, 513.

(12) Baldwin's rules for ring closure indicate that 5-*exo-tet* processes are favored, whereas 6-*endo-tet* processes are disfavored: (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. However, epoxides are borderline cases that lie between purely tetrahedral and purely trigonal systems because of their strained bonds. Consequently, their behavior in ring closures is more difficult to predict; see: (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; pp 165–171. For other recent examples of 5-*exo-tet* closures of epoxides and amide anions, see: (c) Takahata, H.; Banba, Y.; Tajima, M.; Momose, T. *J. Org. Chem.* **1991**, *56*, 240.

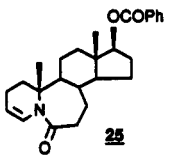
(13) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(14) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, 1969; pp 238–241 and 286–289.

Scheme III



to the corresponding ring-contracted A-nor products, as shown in Scheme II. These unexpected processes were accompanied by competing substitution at C-3 with inversion of configuration. Conditions for these reactions, the specific starting materials employed, and the products observed are summarized in Table I. Several features are apparent from these data. First, there was no crossover between the 3α- and 3β-series, indicating a high degree of stereospecificity in both the rearrangement and the direct substitution reactions. Second, of the four types of conditions investigated, the treatment of the alcohols **4** and **5** with thionyl chloride and the reaction of the chlorides **19** and **20** with aqueous silver nitrate afforded predominantly the products of rearrangement. In the former case, the formation of chlorosulfites[15] provided the necessary leaving group at C-3. The possibility that rearrangement occurred by prior formation of the corresponding 3-chloro derivatives via a stereospecific S_Ni reaction of the chlorosulfites with retention of configuration was ruled out by the observation that authenic samples of the chlorides **19** and **20** were recovered intact when subjected to identical conditions in a control experiment. The reactions of tosylates **17** and **18** with lithium chloride in acetone/2-methyl-2-propanol proceeded chiefly via rearrangement in the case of the 3α-isomer **17**, but mainly by substitution with the 3β-tosylate **18**. Only the use of triphenylphosphine and carbon tetrachloride resulted predominantly in substitution[16] in both **4** and **5** to afford **20** and **19**, respectively, along with a small amount of the elimination product **25** in the case of the 3α-isomer **4**. This



25

reaction therefore also served as the best method of preparation of the 3-chloro derivatives, which were required for the silver nitrate-promoted rearrangements listed in Table I, and for further studies described below. Third, we note that the reactions in the 3α-series proceeded more rapidly, afforded higher yields of rearranged products, and/or produced higher ratios of rearrangements vs substitution in all four types of processes.

The inversion of configuration observed during the formation of the substitution products in Scheme II suggests that they are formed by a direct S_N2 displacement that does not involve neighboring-group participation by the lactam nitrogen atom. In contrast, a more complex explanation is required for the stereospecific ring contractions observed under the diverse reaction conditions in Table I. The observed stereospecificity rules out an S_N1 reaction proceeding via the initial formation of a carbocation intermediate, followed by subsequent rearrangement (Scheme III, top pathway), as this pathway would produce identical mixtures of stereoisomers from both the 3α- and 3β-starting materials. The stereochemistry of S_N1-like reactions can also be affected by ion pairs,[17a] whose formation and behavior are generally dependent on factors such as solvent polarity and the nature of the ions themselves. The complete stereospecificity observed in the present rearrangement under all of the conditions of Table I, including different solvents and leaving groups, is not consistent with ion pair formation as a complete explanation for the stereochemical outcome. The observed stereochemistry would be expected from an initial attack of the nucleophile Y^- at C-4 with displacement of the amide anion, followed by reclosure of the A-ring via S_N2 attack by the nitrogen atom at C-3 (Scheme III, bottom pathway). However, N-dealkylation of amides or lactams is not a facile process, and strong nucleophiles generally attack the acyl carbon atom preferentially. Furthermore, this pathway is incompatible with the particularly clean rearrangements observed in aqueous silver nitrate, where the reaction is facilitated by the halophilic Ag^+ cation,[17b] which presumably acts as a Lewis acid.

A more satisfactory and consistent mechanism invokes neighboring-group participation by the nitrogen atom in the displacement of the leaving group X from C-3, resulting in the stereospecific formation of aziridinium ions **26** and **27** in the 3α- and 3β-series, respectively (Scheme IV). Attack at C-4 by the nucleophile Y^- then affords the corresponding ring-contracted products. Stereoelectronic considerations require an equatorial leaving group at C-3 in order to provide a favorable alignment of the p-orbital containing the nitrogen lone pair with the C–X bond. This condition is met in the 3β-series if one assumes the usual chair conformation for the A-ring of the substrate. However, the axial C–X bond in the 3α-derivatives provides an unsatisfactory alignment for the formation of the aziridinium ion **26**. By analogy, the solvolyses of cholesterol derivatives containing equatorial leaving groups at C-3 proceed via neighboring group participation by the Δ^5 π-system, resulting in the stereospecific formation of 3β-substituted products **28** and 6β-substituted 3,5-cyclosteroids **29** (Scheme V).[18,19] In contrast, the corresponding axially-substituted epimers are not subject to neighboring-group participation and react via other pathways.[20]

In order to rationalize the stereospecific rearrangement of the 3α-substituted azasteroids, we propose that ring-flipping to the corresponding boat conformation occurs prior to aziridinium ion formation, thereby placing the leaving group in a more favorable pseudoequatorial position. This assumption is supported by molecular mod-

(15) The reaction of **4** with thionyl chloride in pyridine produced 32% of **21** and 4% of **20**. Under similar conditions, **5** afforded 41% of **19**, no rearrangement product **22**, and a substantial amount (>30%) of a product tentatively identified as the corresponding sulfite. The treatment of cholesterol with thionyl chloride under similar conditions also affords the corresponding sulfite derivative: Daughenbaugh, P. J.; Allison, J. B. *J. Am. Chem. Soc.* **1929**, *51*, 3665.

(16) The conversion of other types of alcohols into chlorides by this method is known to give chiefly substitution products with inversion of configuration and a minimum of rearrangement: (a) Weiss, R. G.; Snyder, E. I. *J. Org. Chem.* **1971**, *36*, 403. (b) Snyder, E. I. *J. Org. Chem.* **1972**, *37*, 1466.

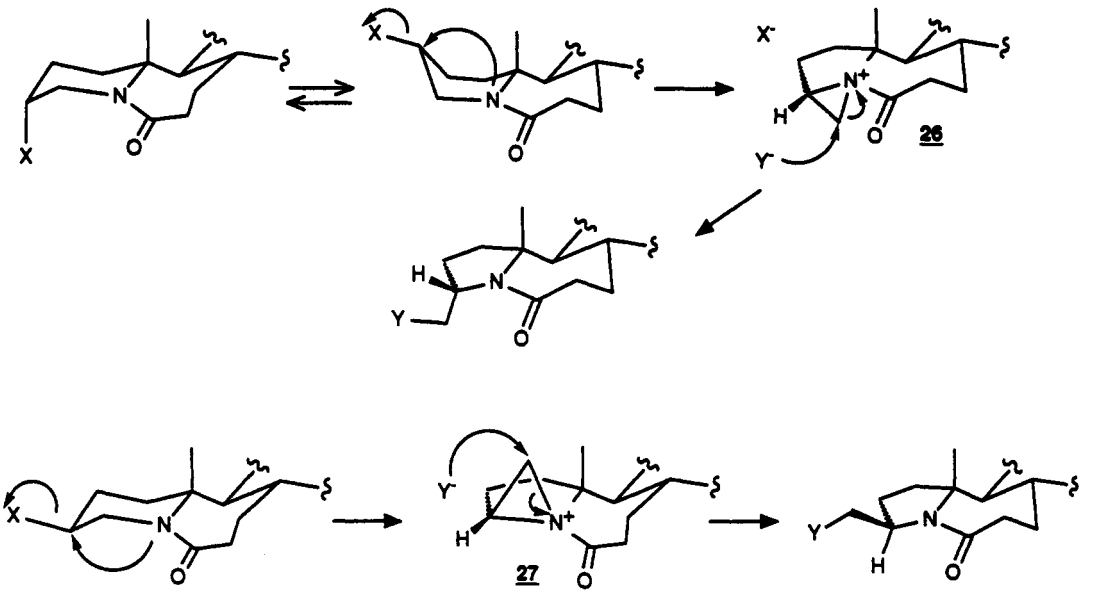
(17) (a) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 2nd ed.; Harper & Row: New York, 1981; Chapter 4. (b) Control experiments employing aqueous THF in the absence of silver nitrate resulted in the recovery of the starting materials **19** and **20**.

(18) Winstein, S.; Adams, R. *J. Am. Chem. Soc.* **1948**, *70*, 838.

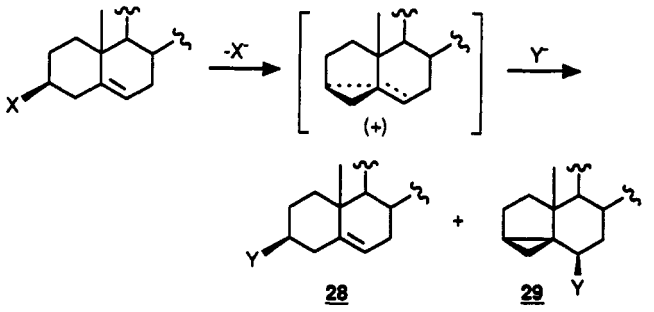
(19) For a review of this and related solvolyses, see: Kirk, D. N.; Hartshorn, M. P. In *Steroid Reaction Mechanisms*; Eaborn, C., Chapman, N. B., Eds.; Elsevier: Amsterdam, 1968; Chapter 5.

(20) King, L. C.; Bigelow, M. J. *J. Am. Chem. Soc.* **1952**, *74*, 6238.

Scheme IV



Scheme V



eling,[21a] which indicates that the boat conformations for the 3α-series are less stable than the corresponding chairs by only 0.1, 0.4, and 1.3 kcal/mol for X = OH, OTs, and Cl, respectively. It is interesting to note that the X-ray crystal structures of **19** and **20** (vide infra) reveal that the A-ring of the 3α-isomer exists in the boat conformation in the solid state, whereas the 3β-analogue exists as the expected chair.

Variable-temperature ^{1}H-NMR experiments performed with the 3α-chloro derivative **19** in CD_2Cl_2 solution provided further information about its conformational behavior (see Figure 1). At or below 200 K the proton at C-3 produced two distinct signals at δ 4.36 and 4.24, integrating in the ratio of 2.2:1. These are assigned to the

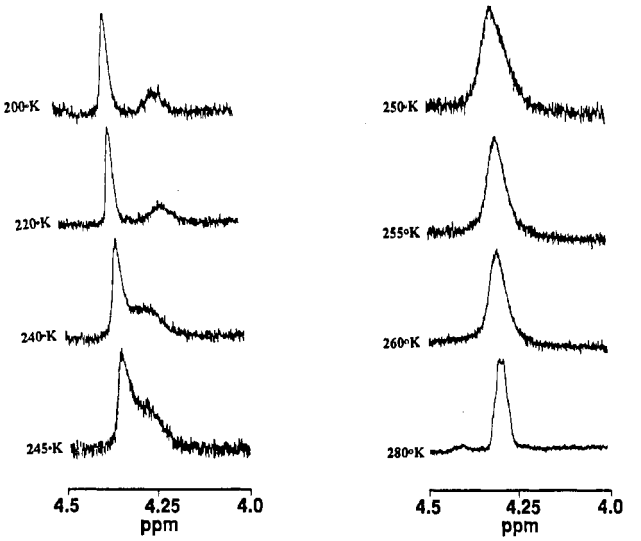


Figure 1. Low-temperature ^{1}H-NMR spectra of **19** showing H(3).

equatorial C-3 proton of the chair conformation and the pseudoaxial proton of the corresponding boat, respectively, on the basis of the upfield resonance and broader shape, due to diaxial couplings with protons at C-2 and C-4, of the signal at δ 4.24.[14] Coalescence of the two signals was observed upon warming to 250 K, indicating an activation energy (ΔG^*) of 12.2 kcal/mol for the ring-flipping process,[22] and a value of ΔG = 0.3 kcal/mol derived from the integrated intensities.

Although the stereospecificity of the above rearrangements argues strongly in favor of neighboring group participation, we performed a series of solvolysis experiments in aqueous silver nitrate solution in order to further test this assumption. The relative rates of reaction of compounds **19** and **20** were compared with those of 3α- and 3β-chloro-5α-cholestanes (**30** and **31**, respectively), which lack both heteroatoms with lone pairs and π-systems capable of assisting chloride departure. 3β-Cholesteryl chloride (**32**) was also included in order to compare the anchimeric assistance rendered by the lactam nitrogen atoms of **19** and **20** with that from the Δ^5 double bond of

(21) (a) Molecular modeling was performed with MACROMODEL Version 3.1 X (Columbia University, 1990). Minimizations employed the MM2 force field and the PRCG subroutine. A full conformational search using the Monte Carlo method contained in MACROMODEL was carried out in the case of compounds **19** and **20**. This confirmed that the A-chair B-**37** conformation represents the global energy minimum for each of these compounds, as indicated in Table II. MO calculations on the optimized geometries of **19** and **20** were performed with MOPAC Version 6.0 (U.S. Air Force Academy, Colorado Springs), using the AM1 Hamiltonian, and confirmed that the A-chair B-ring **37** is the most stable of the four conformations listed in Table II in the case of both **19** and **20** and that the B-ring **38** is more stable than **37** when associated with the A-boat conformation. However, the MO calculations produced greater values of ΔG(boat–chair) than those obtained by molecular modeling and shown in Table II (5.1 vs 1.3 and 8.4 vs 3.4 kcal/mol for **19** and **20**, respectively). There was also generally close agreement between structures derived by modeling and those obtained by X-ray diffraction for these compounds. (b) Molecular modeling was performed with PC MODEL Version 1.0 (Serena Software) in the MMX mode. All energies reported in our preliminary communication (ref 8) were obtained this way. The energies for ions **26** and **27** in Scheme IV should be regarded with appropriate reservation because of inherent limitations in the force fields used in their calculation.

(22) Lambert, J. B.; Shurvell, H. F.; Lightner, D.; Cooks, R. G. *Introduction to Organic Spectroscopy*; Macmillan: New York, 1987; p 100.

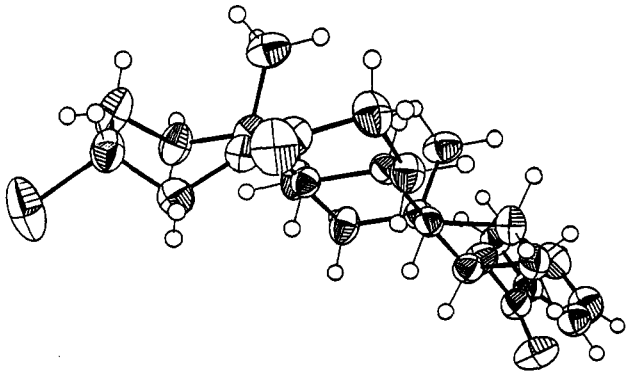
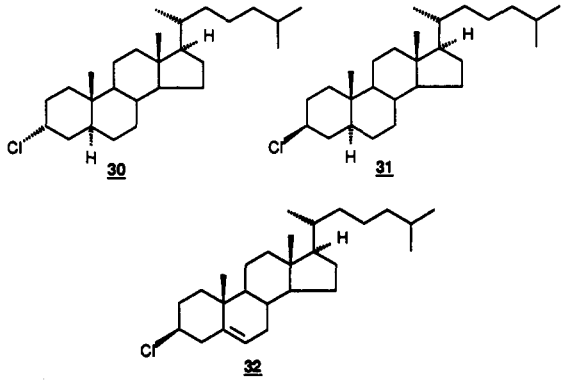


Figure 2. Drawing of **19** made with the program ORTEPII.[36]

32 (i.e., as in Scheme V). The solvolyses were carried out under identical conditions and monitored by TLC and ^{1}H-NMR. The order of reactivity was determined to be **19** > **32** > **30** > **20** > **31**. The more rapid solvolyses of the azasteroids compared to the corresponding chlorocholestanes of the same configuration at C-3 (i.e., 3α-**19** > 3α-**30** and 3β-**20** > 3β-**31**) is consistent with our assumption of participation by the lactam nitrogen atom. It is interesting to note, however, that 3β-cholesteryl chloride **32** proved to be more reactive than the 3β-azasteroid **20**, suggesting that anchimeric assistance from the nitrogen atom of the latter is less effective than that from the carbon–carbon double bond of the former. The delocalization of the nitrogen lone pair by the carbonyl group no doubt substantially diminishes its availability for this purpose.



30 **31** **32**

The relatively low nucleophilicity of the lactam nitrogen atom in the azasteroids and the destabilizing effect of the carbonyl moiety upon the formation of fully-developed aziridinium ion intermediates **26** and **27** may result in some degree of concertedness in these rearrangements, as shown in the transition states **33** and **34**. Stereoelectronic considerations of a concerted process require an antiperiplanar alignment of the C(3)–X bond with the C(4)–N bond.[23a] This demand is met in the predominant chair conformation of the A-ring of compounds in the 3β-series and would again be ensured by prior ring-flipping to the boat conformation in the corresponding 3α-epimers. The extent of concertedness is expected to depend upon the specific nature of X, Y and the reaction conditions, where good leaving groups and weak nucleophiles favor early C(3)–X cleavage and the formation of fully-developed aziridinium

(23) (a) See ref 12b, pp 182–190. (b) A reviewer has pointed out that the concerted reaction would involve a pseudopericyclic transition state, as defined by: Ross, J. A.; Seiders, R. P.; Lemal, D. M. *J. Am. Chem. Soc.* **1976**, *98*, 4325. Such processes were subsequently subjected to criticism and must therefore be regarded with appropriate reservation. See: Snyder, J. P.; Halgren, T. A. *J. Am. Chem. Soc.* **1980**, *102*, 2861.

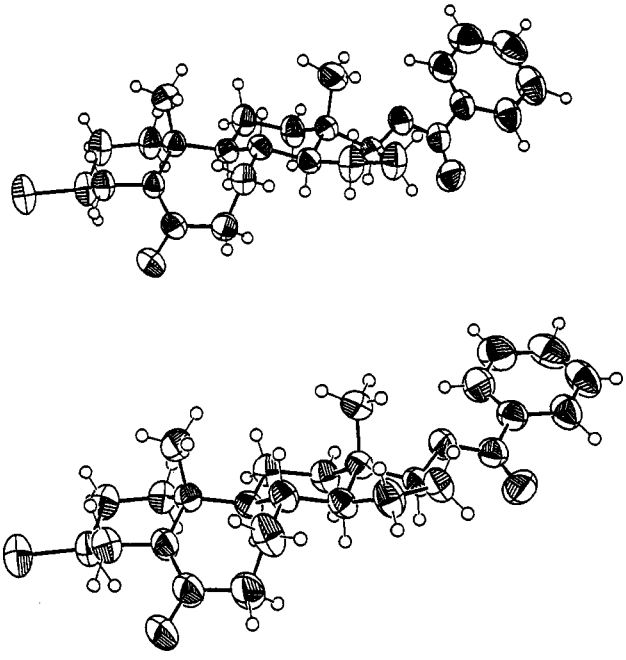
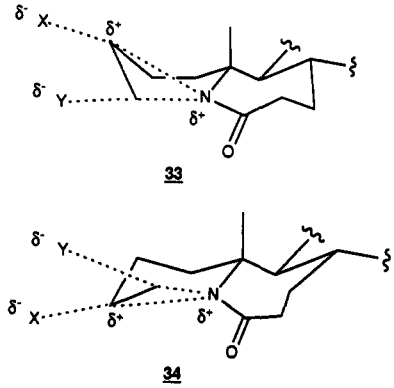


Figure 3. Drawing of **20i** (top) made with the program ORTEPII.[36] Drawing of **20ii** (bottom) made with the program ORTEPII.[36]

ion intermediates, while strong nucleophiles and poorer leaving groups favor earlier formation of the C(4)–Y bond with a corresponding increase in the degree of concertedness.[23b]



33

34

Conformational Studies. The consistently greater reactivity of azasteroids containing nucleofugal groups in the 3α- compared to the 3β-position also requires explanation. This difference in the two series is evident from the relative rate comparisons described above and from the considerably longer reaction times required for the 3β-compounds, as indicated in Table I. The more rapid solvolysis of the axially-substituted 3α-cholestanyl tosylate relative to the equatorial 3β-isomer has been attributed[24] to greater relief of steric crowding during carbonium ion formation in the former case. However, as explained earlier, carbonium ion formation in the present work was ruled out by the observed stereospecificity. Furthermore, there is a facile interconversion between the boat and chair conformers of the 3α-substituted azasteroids, and reaction through the former is required on stereoelectronic grounds. We therefore performed molecular modeling studies of variously 3α- and 3β-substituted azasteroids and obtained X-ray crystal structures of the 3α- and 3β-chloroazasteroids **19** and **20** in order to identify conformational features that could account for the observed differences in their reaction

(24) Nishida, S. *J. Am. Chem. Soc.* **1960**, *82*, 4290.

Table II. Molecular Modeling of 3-Substituted 5-Azasteroids

compd	C-3 substituent	A-ring conformation	B-ring 37 energy (kcal/mol)	B-ring 38 energy (kcal/mol)	ΔG (37–38) (kcal/mol)	ΔG (boat–chair)[a] (kcal/mol)
4	α-OH	chair	73.0	75.3	−2.3	0.1
4	α-OH	boat	76.2	73.1	3.1	
5	β-OH	chair	71.4	73.9	−2.5	1.6
5	β-OH	boat	78.2	73.0	5.2	
17	α-OTs	chair	111.4	113.8	−2.4	0.4
17	α-OTs	boat	114.8	111.8	3.0	
18	β-OTs	chair	110.5	113.1	−2.6	2.9
18	β-OTs	boat	118.0	113.4	4.6	
19	α-Cl	chair	77.5	80.2	−2.7	1.3
19	α-Cl	boat	81.8	78.8	3.0	
20	β-Cl	chair	76.4	79.1	−2.7	3.4
20	β-Cl	boat	84.9	79.8	5.1	
21	α-Cl		77.2	73.3	3.9	
22	β-Cl		78.9	78.1	0.8	

[a] The difference between the more stable boat and the more stable chair is shown.

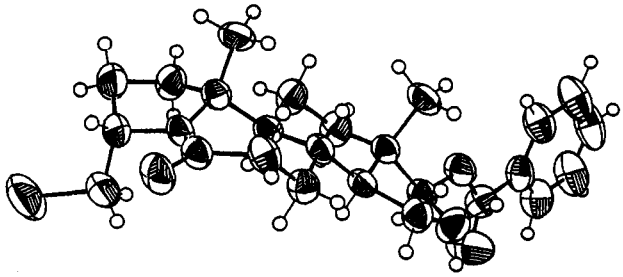


Figure 4. Drawing of 21 made with the program ORTEPII.[36]

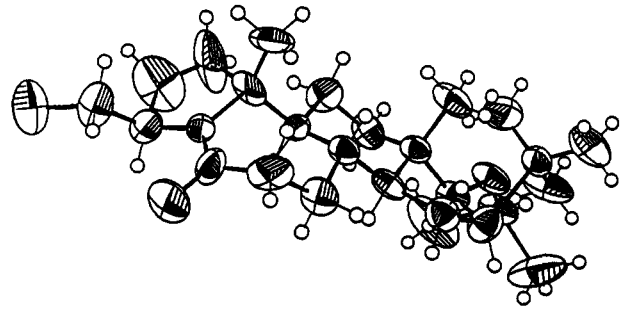
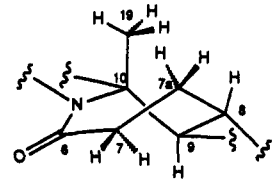


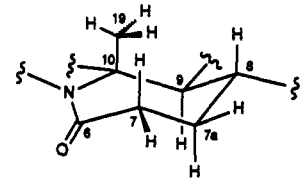
Figure 5. Drawing of 36 made with the program ORTEPII.[36]

rates. X-ray structures of the A-nor products 21 and 36[25] were also determined in order to verify the stereochemistry at C-3. These are shown in Figures 2–5, respectively.

Molecular modeling of the 3α-compounds 4, 17, and 19 indicated slightly more stable chair conformations for their A-rings,[21a] with differences of 0.1, 0.4, and 1.3 kcal/mol, respectively, as indicated in Table II. The differences in energies between the A-chair and A-boat were greater (1.6, 2.9, and 3.4 kcal/mol, respectively) in the 3β-compounds 5, 18, and 20. Destabilization of the chair by dipole–dipole interactions between the axial 3-substituent and the carbonyl group may account for the relatively small differences in energy between the boat and chair forms in the 3α-series. However, we also noted that conformational transmission between the A-ring and the B-ring strongly affected the conformation of the latter. In each example, the A-chair was accompanied by a B-ring in which C-7 and C-7a occupied positions below and above the plane of the molecule, respectively, with a pseudoequatorial 7β-hydrogen and a pseudoaxial 7aβ-hydrogen atom, as in structure 37. In contrast, A-boats were accompanied by flipping of the corresponding B-rings, resulting in pseudoaxial 7β- and pseudoequatorial 7aβ-hydrogens, as in structure 38. The relative stabilities of these conformations are also given in Table II. Conformation 38 was also more stable than 37 in the A-nor compounds 21 and 22.



37



38

The X-ray crystal structures of the 3-chloro derivatives 19 and 20 and of the A-nor analogues 21 and 36 confirmed the predictions concerning the B-ring conformations derived from molecular modeling. Moreover, crystallization of the 3α-derivative 19 occurred in the A-boat form, despite the greater stability of the corresponding chair conformation that was predicted by molecular modeling and demonstrated in solution by the low-temperature NMR experiments described earlier. We conclude that crystal-packing forces favor the A-boat and are sufficiently strong to overcome the otherwise normal preference for the chair conformation. We also observed that two slightly different conformations of the 3β-chloro derivative, designated 20i and 20ii, cocrystallized.

The X-ray structure of the boat conformation of 19 (Figure 2) provides further insight into conformational effects that explain why it rearranges more rapidly than

(25) Of the 3-chloro-A-nor-17-benzoates 21 and 22, only the former compound afforded suitable crystals for X-ray crystallography. Consequently, the 17-silyl ether analogues 35 and 36 were also prepared (Scheme I) and 36 was used instead of 22 for X-ray studies.

Table III. H–H Contacts of <2.20 Å in Compounds 19, 20i, and 20ii

	19	20i	20ii
$H_{1\alpha}$–$H_{4\alpha}$	2.17 (3)		
$H_{1\alpha}$–$H_{11\alpha}$		2.18 (4)	
$H_{1\beta}$–$H_{11\alpha}$	2.18 (3)	2.05 (4)	2.04 (4)
$H_{2\beta}$–H_3	2.14 (4)		
H_3–$H_{4\alpha}$			2.11 (5)
$H_{7\alpha}$–H_9		2.16 (4)	2.11 (5)
$H_{7\beta}$–$H_{7a\alpha}$		2.17 (4)	
$H_{7\beta}$–H_{19}	1.98 (4)		
$H_{15\beta}$–$H_{16\beta}$		2.13 (5)	
$H_{15\beta}$–H_{18}		2.16 (6)	
$H_{16\alpha}$–H_{17}		2.17 (4)	

its 3β-A-chair isomer **20i,ii** (Figures 3i and 3ii). In **19**, the A-ring boat is accompanied by a B-ring of type **38** and a particularly short contact (1.98 (4) Å) between the axial 7β-hydrogen and one of the C-19 angular methyl hydrogens. No similar short contacts of <2.00 Å are present in **20**, where the A-chair of each of the two crystal forms is accompanied by a B-ring of type **37**, in which the 7β-hydrogen is equatorial. A summary of the shortest contacts in compounds **19** and **20** is presented in Table III. As each of the two compounds proceeds along the reaction coordinate toward its respective aziridinium ion intermediate, pyramidalization of the nitrogen atom and decreasing π-overlap in the amide bond permit torsion in the B-ring that increases the distance between the 7β- and 19-hydrogens in **19**. Thus, the greater relief of steric crowding in the reaction of **19** may contribute to its faster reaction rate compared to **20**. Furthermore, molecular modeling[21b] indicates that the aziridinium ion **26** (Scheme IV), produced from 3α-precursors such as **19**, is 4.8 kcal/mol more stable than its counterpart **27**, produced from β-precursors such as **20**. Thus, if the transition states resemble the aziridinium ions more closely than the original starting materials in these rearrangements, then this too could contribute to the faster reactions observed in the 3α-series.

The strength of the amide resonance in compounds **19** and **20** is expected to play a significant role in determining the extent of anchimeric assistance afforded by the nitrogen atom, as delocalization diminishes the availability of its lone pair. Furthermore, amide resonance is known to affect physicochemical and spectral properties such as the infrared frequencies associated with this functional group.[26] The infrared spectra of **19** and **20** show the carbonyl stretch at 1628 and 1630 cm^{-1}, respectively. This is considerably lower than the value of 1670–1672 cm^{-1} reported for typical 7-membered lactams[27] and suggests an unusually low bond order for the carbonyl group, in turn implying an exceptionally strong amide resonance. However, the X-ray structures of these compounds reveal that the N–C(6) and C=O bond lengths are not abnormal[28] and that although the nitrogen atom lies very close to the C(4)–C(6)–C(10) plane, the dihedral angles (C4)–N–C(6)–O are −13.83°, 13.85°, and 14.29° in **19**, **20i**, and **20ii**, respectively. This indicates significant torsion of the amide linkage and a slight weakening of the π-overlap required for effective amide resonance. We therefore attribute the low IR frequencies to the existence of two additional rings (A and C) fused to the lactam ring[27b] and not to abnormally strong amide resonance. Moreover, the decrease in the effectiveness of the amide resonance as a result of torsion is expected to enhance neighboring-group participation by the nitrogen in reactions at C-3.

Table IV. Selected Bond Lengths and Bond Angles in Azasteroids 19, 20i, and 20ii

	19	20i	20ii
bond lengths (Å)			
N–C(6)	1.365 (3)	1.358 (4)	1.349 (5)
C(6)–O	1.226 (3)	1.228 (4)	1.227 (4)
bond angles (deg)			
C(4)–N–C(6)	116.6 (2)	114.5 (2)	114.1 (3)
C(4)–N–C(10)	116.2 (2)	114.8 (2)	115.0 (3)
C(6)–N–C(10)	126.2 (2)	129.4 (2)	130.5 (3)
dihedral angles (deg)			
C(4)–N–C(6)–O	−13.83	13.85	14.29
C(10)–N–C(6)–O	168.02	−151.94	−158.65
N–C(4)–C(3)–Cl	170.36	175.33	174.91
ΔN plane[a] (Å)	−0.013	0.097	0.309

[a] Distance of N atom from plane of C(4)–C(6)–C(10).

The N–C(4)–C(3)–Cl dihedral angles in **20i** and **20ii** (175.33° and 174.91°, respectively) are closer to the required antiperiplanar conformation than that of **19** (170.36°). This further emphasizes the importance of the B-ring conformation in determining the relative reactivities of the 3α- and 3β-isomers, since **19** exhibits the faster rearrangements, despite its greater departure from the stereoelectronically ideal A-ring geometry. Selected bond lengths and bond angles for compounds **19**, **20i**, and **20ii** are given in Table IV.

Conclusions

B-Homo-5-azasteroid lactams containing leaving groups in the 3-position undergo stereospecific rearrangements to the corresponding ring-contracted A-nor analogues, as well as competing substitution reactions with inversion of configuration at C(3). These results are in accord with a mechanism involving neighboring-group participation by the nitrogen atom in the departure of the C(3) nucleofuge with the formation of the corresponding aziridinium ion intermediates. Compounds in the 3β-series react via the A-ring chair conformation, where the leaving group occupies an equatorial position. On the other hand, the leaving group is axial in the A-chair of the 3α-series and stereoelectronic considerations require ring-flipping to the A-boat in order to permit neighboring-group participation. Molecular modeling, X-ray crystallographic, and variable-temperature ^{1}H-NMR studies indicate that the A-chair conformations are considerably more stable than the A-boats in the 3β-substituted compounds and only slightly more so in the 3α-analogues, and the A-boat is unexpectedly favored in the solid state of the 3α-chloro derivative. Dipole repulsion between the axial 3α-substituent and the carbonyl group may destabilize the chair conformation and so render the corresponding boat more energetically competitive. The A-chair and A-boat forms are associated with substantially different B-ring conformations, where a destabilizing H–H contact of 1.98 Å between hydrogens at C(7β) and C(19) exists in the A-boat conformer of the 3α-chloro derivative. This, together with the greater stability of the aziridinium ion obtained from 3α-compounds, accounts for the greater facility of the rearrangements in the 3α-series. Since substituents at C(3) are of particular importance in the recognition and binding

(26) Bennet, A. J.; Somayaji, V.; Brown, R. S.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1991**, *113*, 7563.

(27) (a) Williams, D. H.; Fleming, I. *Spectroscopic Methods in Organic Chemistry*; McGraw Hill: London, 1973; p 58. (b) Bellamy, L. J. *The Infrared Spectra of Complex Molecules*, 3rd ed.; Chapman and Hall: London, 1975; p 242.

(28) (a) A search for seven-membered, N-substituted lactams in the Cambridge Crystallographic Database (ref 28b) found five independent observations which had an average C=O distance of 1.234 (9) Å and N–C(6) distance of 1.33 (1) Å. REFCODES and detailed geometry are in the supplementary material. (b) Allen, F. H.; Kennard, O.; Taylor, R. *Acc. Chem. Res.* **1983**, *16*, 146.

of steroid hormones by the active sites of receptors and enzymes, these studies suggest that the nitrogen atom of 5-azasteroids could have profound effects upon their biological properties by altering the reactivity at this crucial position.

Experimental Section

Melting points were determined on an A. H. Thomas hot-stage apparatus and are uncorrected. IR spectra were recorded on Nicolet 5DX or Mattson 4030 spectrometers. ^1H and ^{13}C NMR spectra were recorded on a Bruker ACE 200 spectrometer, using deuteriochloroform as the solvent, with either chloroform or tetramethylsilane as the internal standard, unless otherwise noted. Certain other spectra that were obtained on a Bruker AM 400 instrument, or in other solvents, are so indicated. Mass spectra were obtained by electron impact on a Kratos MS80 or a VG 7070 spectrometer by Dr. Q. Wu. Elemental analyses were determined by Ms. D. Fox at the University of Calgary. Preparative TLC was carried out on Analtech 20- × 20-cm glass plates coated with 1 mm of silica gel GF and analytical TLC on Merck silica gel 60 F-254 sheets. Flash chromatography was performed on Merck silica gel, 60–200 mesh. Testosterone was purchased from the Sigma Co., and all other reagents were commercially available and purified by standard procedures as required.

17β-Hydroxy-4,5-secoandrost-3-yn-5-one *tert*-Butyldimethylsilyl Ether (8a). 17β-Hydroxy-4,5-secoandrost-3-yn-5-one[11] (7) was prepared from testosterone and converted into the *tert*-butyldimethylsilyl ether[29] **8a** in 78% yield. The product was purified by flash chromatography (elution with 10% ethyl acetate–hexane) and crystallization from methanol–water, mp 78–78.5 °C: IR (Nujol) 3311, 2116, 1705, 1083 cm^{-1}; ^1H-NMR δ 3.59 (t, J = 8.0 Hz, 1 H), 2.54 (dt, J = 6.3, 14.4 Hz, 1 H), 1.10 (s, 3 H), 0.90 (s, 9 H), 0.78 (s, 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H); mass spectrum m/z (relative intensity) 402 (M$^+$, 3), 345 (100), 269 (14), 75 (75). Anal. Calcd for $C_{25}H_{42}O_2Si$: C, 74.56; H, 10.51. Found: C, 75.07; H, 10.48.

17β-Hydroxy-4,5-secoandrost-3-yn-5-one Benzoate (8b). The alcohol **7**[11] was treated with benzoyl chloride in pyridine in the presence of a catalytic amount of 4-(*N*,*N*-dimethylamino)-pyridine (DMAP) at room temperature for 12 h to afford the benzoate **8b**, mp 150–151 °C (from dichloromethane–hexane): IR (film) 3304, 2116, 1715, 1705 cm^{-1}; ^1H-NMR δ 8.08–8.03 (m, 2 H), 7.58–7.42 (m, 3 H), 4.88 (dd, J = 9.1, 7.4 Hz, 1 H), 2.57 (dt, J = 14.4, 6.2 Hz, 1 H), 1.12 (s, 3 H), 1.02 (s, 3 H); mass spectrum m/z (relative intensity) 392 (M$^+$, 13), 341 (49), 340 (76), 325 (27), 105 (100). Anal. Calcd for $C_{26}H_{32}O_3$: C, 79.56; H, 8.22. Found: C, 79.67, H, 8.31.

17β-Hydroxy-5-aza-4,5-seco-*B*-homoandrost-3-en-6-one *tert*-Butyldimethylsilyl Ether (10a). The keto acetylene **8a** (2.07 g, 5.15 mmol) was hydrogenated at ca. 1 atm of pressure in the presence of 0.8 g of quinoline and 0.6 g of 5% Pd on $CaCO_3$ catalyst poisoned with lead (Aldrich) in 40 mL of 95% ethanol. After 1.5 h, the mixture was filtered through Celite, concentrated, dissolved in ethyl acetate, washed with 10% aqueous HCl and then with $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated in vacuo to afford 2.05 g (99%) of the olefin **9a** as a light brown oil:[30] IR (film) 1707, 1641, 1136, 1087, 836 cm^{-1}; ^1H-NMR δ 5.91–5.71 (m, 1 H), 5.04–4.67 (m, 2 H), 3.58 (t, J = 8.1 Hz, 1 H), 2.53 (dt, J = 6.3, 14.5 Hz, 1 H), 2.27 (ddd, J = 14.7, 4.6, 2.4 Hz, 1 H), 1.09 (s, 3 H), 0.89 (s, 9 H), 0.77 (s, 3 H), 0.022 (s, 3 H), 0.016 (s, 3 H); mass spectrum m/z (relative intensity) 404 (M$^+$, <1), 347 (25), 271 (14), 75 (100).

The crude olefin **9a** (2.05 g, 5.07 mmol) and hydroxylamine hydrochloride (744 mg, 10.7 mmol) were refluxed for 1.5 h in 10 mL of methanol and 10 mL of pyridine. The mixture was then diluted with ether, washed repeatedly with 10% aqueous HCl and then with $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated in vacuo to afford 2.03 g (96%) of the crude oxime as a solid white foam: IR (film) 3304, 1638, 1139, 1006 cm^{-1}; ^1H-NMR δ 5.89–5.69 (m, 1 H), 5.01–4.85 (m, 2 H), 3.56 (t, J = 8.0 Hz, 1 H), 3.34 (dd, J = 13.8, 3.9 Hz, 1 H), 2.18 (m, 1 H), 1.08 (s, 3 H), 0.89 (s, 9 H), 0.74 (s, 3 H), 0.02 (s, 3 H), 0.01 (s, 3 H).

The above oxime (1.46 g, 3.48 mmol), *p*-toluenesulfonyl chloride (1.68 g, 8.80 mmol), and DMAP (0.12 g, 1.0 mmol) were dissolved in 15 mL of dry pyridine and heated at 65 °C for 4 h. The pyridine was removed as in the previous procedure, and the residue was separated by flash chromatography[31] (elution with ethyl acetate) to afford 0.77 g (53%) of lactam **10a**, mp 129–131 °C (from methanol–water): IR (film) 3220, 3076, 1651, 1140, 1085, 835 cm^{-1}; ^1H-NMR δ 5.86–5.66 (m, 1 H), 5.60 (br s, 1 H), 5.10–4.98 (m, 2 H), 3.56 (t, J = 8.1 Hz, 1 H), 2.51 (m, 2 H), 1.34 (s, 3 H), 0.88 (s, 9 H), 0.75 (s, 3 H), 0.02 (s, 6 H); mass spectrum m/z (relative intensity) 419 (M$^+$, 5), 378 (17), 362 (48), 265 (17), 98 (100), 75 (98). Anal. Calcd for $C_{25}H_{45}NO_2Si$: C, 71.54; H, 10.81; N, 3.34. Found: C, 71.49; H, 10.85; N, 3.24.

17β-Hydroxy-5-aza-4,5-seco-*B*-homoandrost-3-en-6-one Benzoate (10b). The keto acetylene **8b** was hydrogenated as in the case of **8a** to afford the olefin **9b** in quantitative yield, mp 63–64 °C (from hexane): IR (film) 1715, 1640, 1277, 1115 cm^{-1}; ^1H-NMR δ 8.09–8.04 (m, 2 H), 7.63–7.43 (m, 3 H), 5.94–5.74 (m, 1 H), 5.06–4.85 (m, 3 H), 2.57 (dt, J = 6.2, 14.4 Hz, 1 H), 1.12 (s, 3 H), 1.02 (s, 3 H); mass spectrum m/z (relative intensity) 394 (M$^+$, 3), 341 (45), 340 (64), 325 (31), 105 (100). Anal. Calcd for $C_{26}H_{34}O_3$: C, 79.14; H, 8.69. Found: C, 79.45; H, 8.84.

The olefin **9b** was treated similarly to **9a** and produced a crystalline oxime, mp 139–140 °C (from ethyl acetate–hexane) in 81% yield: IR (Nujol) 3269, 1715, 1642, 1275, 1115 cm^{-1}; ^1H-NMR δ 8.08–8.03 (m, 2 H), 7.61–7.41 (m, 3 H), 5.91–5.74 (m, 1 H), 5.05–4.82 (m, 3 H), 3.41–3.32 (m, 1 H), 2.37–2.01 (m, 2 H), 1.10 (s, 3 H), 0.98 (s, 3 H). This was subjected to Beckmann rearrangement as in the preparation of **10a** to afford the lactam **10b** in 45% yield, mp 143–144 °C (from methanol–hexane): IR (Nujol) 3206, 3065, 1716, 1652, 1273 cm^{-1}; ^1H-NMR δ 8.08–8.02 (m, 2 H), 7.61–7.41 (m, 3 H), 5.86–5.66 (m, 1 H), 5.63 (br s, 1 H), 5.10–4.97 (m, 2 H), 4.89 (t, J = 8.4 Hz, 1 H), 2.55 (m, 2 H), 1.36 (s, 3 H), 0.98 (s, 3 H); mass spectrum m/z (relative intensity) 409 (M$^+$, 2), 368 (12), 354 (10), 105 (100). Anal. Calcd for $C_{26}H_{35}NO_3$: C, 76.25; H, 8.61; N, 3.42. Found: C, 76.53; H, 8.92; N, 3.53.

3,4-Epoxy-17β-hydroxy-5-aza-4,5-seco-*B*-homoandrostan-6-one *tert*-Butyldimethylsilyl Ether (11a). Lactam **10a** (923 mg, 2.20 mmol) and *m*-CPBA (1.05 g of ca. 80% purity, ca. 4.87 mmol) were dissolved in 30 mL of chloroform. After 36 h, the mixture was concentrated, diluted with ethyl acetate, washed with aqueous K_2CO_3 and then with aqueous NaCl, dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography (elution with ethyl acetate) to afford 881 mg (92%) of **11a** as a white solid foam (mixture of diastereomers): IR (film) 3288, 3222, 3067, 1651, 1140, 1087, 837 cm^{-1}; ^1H-NMR δ 5.61 (br s, 1 H), 3.55 (t, J = 8.1 Hz, 1 H), 2.87 (m, 1 H) and 2.77 (t, J = 8.8 Hz, 1 H), 2.50 (m, 3 H), 1.35 (s, 3 H), 0.87 (s, 9 H), 0.74 (s, 3 H), 0.01 (s, 6 H); mass spectrum m/z (relative intensity) 435 (M$^+$, 6), 404 (75), 378 (35), 265 (17), 114 (62), 75 (100). Anal. Calcd for $C_{25}H_{45}NO_3Si$: C, 68.91; H, 10.41; N, 3.22. Found: C, 68.51; H, 10.36; N, 3.12.

3,4-Epoxy-17β-hydroxy-5-aza-4,5-seco-*B*-homoandrostan-6-one Benzoate (11b). Lactam **10b** was oxidized with *m*-CPBA as in the preceding procedure to afford the epoxide **11b** in 96% yield as a solid (mixture of two diastereomers) after flash chromatography (elution with 1% methanol–chloroform): IR (film) 3289, 3221, 3063, 1715, 1651, 1279, 1117 cm^{-1}; ^1H-NMR δ 8.06–8.02 (m, 2 H), 7.61–7.41 (m, 3 H), 5.70 (br s, 1 H), 4.87 (t, J = 8.1 Hz, 1 H), 2.88 (m, 1 H), 2.78, (t, J = 8.0 Hz, 1 H), 2.52 (m, 3 H), 1.37 (s, 3 H), 0.97 (s, 3 H); mass spectrum m/z (relative intensity) 425 (M$^+$, 10), 407 (28), 395 (55), 394 (93), 105 (100); exact mass calcd for $C_{26}H_{35}NO_4$ 425.2566, found 425.2566.

17β-Hydroxy-3α-(hydroxymethyl)-5-aza-*A*-nor-*B*-homoandrostan-6-one 17β-*tert*-Butyldimethylsilyl Ether (12) and the 3β-Isomer (13). Epoxy lactam **11a** (242 mg, 0.556 mmol) was stirred with sodium hydride (144 mg of 50% dispersion in mineral oil, ca. 3 mmol) in 5 mL of dry THF for 24 h. The reaction was cautiously quenched by the slow addition of water. The

(29) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(30) The product contains a small amount of the alkane formed by overreduction of the acetylene. This is most easily removed at a later stage, after epoxidation of the olefin.

(31) A substantial amount of a less polar byproduct with an IR absorption at 2249 cm^{-1} eluted with 10% ethyl acetate–hexane. This was tentatively identified as the nitrile product of a competing Beckmann fragmentation reaction.

mixture was diluted with ether, washed with aqueous NaCl, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography afforded 209 mg (87%) of the unseparated alcohols **12** and **13**. A portion of this mixture was treated with excess benzoyl chloride in pyridine containing a catalytic amount of DMAP for 6 h. The mixture was diluted with ethyl acetate, washed repeatedly with 10% HCl and then with aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to dryness. The mixture of benzoates was separated by preparative TLC (50% ethyl acetate–hexane). The α-isomer **14** had R_f 0.60: IR (film) 1723, 1633, 1271, 1094 cm^{-1}; ^1H-NMR δ 8.07–8.02 (m, 2 H), 7.57–7.41 (m, 3 H), 4.71 (m, 1 H), 4.46 (dd, J = 10.7, 7.3 Hz, 1 H), 4.25 (dd, J = 10.7, 3.5 Hz, 1 H), 3.48 (t, J = 8.1 Hz, 1 H), 2.60 (m, 2 H), 1.34 (s, 3 H), 0.87 (s, 9 H), 0.72 (s, 3 H), 0.02 (s, 6 H). Irradiation of the peaks at δ 4.46 did not result in NOE enhancement of the peak at δ 1.34 and vice versa. The β-isomer **15** had R_f 0.77: IR (film) 1722, 1633, 1274, 1097 cm^{-1}; ^1H-NMR δ 8.06–8.01 (m, 2 H), 7.56–7.39 (m, 3 H), 4.55 (m, 3 H), 3.56 (t, J = 8.1 Hz, 1 H), 2.56 (m, 2 H), 1.40 (s, 3 H), 0.87 (s, 9 H), 0.74 (s, 3 H), 0.01 (s, 6 H). Irradiation of the peak at δ 4.55 produced substantial enhancement of the signal at δ 1.40 and vice versa.

The α-benzoate **14** was quantitatively saponified by stirring it for 3 h in 5 mL of dioxane containing 2 mL of 1 M NaOH solution. The crude product was recrystallized from chloroform–hexane to afford alcohol **12**, mp 170–171.5 °C: IR (film) 3381, 1608, 1249, 1140, 1092, 835 cm^{-1}; ^1H-NMR δ 4.59 (m, 1 H), 4.08 (br s, exchanged with D_2O, 1 H), 3.77–3.46 (m, 3 H), 2.74–2.53 (m, 2 H), 1.36 (s, 3 H), 0.88 (s, 9 H), 0.75 (s, 3 H), 0.01 (s, 6 H); mass spectrum m/z (relative intensity) 435 (M^+, 4), 404 (100), 378 (14), 114 (57). Anal. Calcd for $C_{25}H_{45}NO_3Si$: C, 68.91; H, 10.41; N, 3.22. Found: C, 68.68; H, 10.26; N, 3.26.

The β-benzoate **15** was treated similarly to afford alcohol **13**, mp 151–152 °C (from chloroform–hexane): IR (film) 3360, 1614, 1249, 1135, 1095, 1084, 835 cm^{-1}; ^1H-NMR δ 5.47 (dd, J = 8.3, 2.6 Hz, exchanged with D_2O, 1 H), 4.20 (m, 1 H), 3.73–3.45 (m, 3 H), 2.70–2.48 (m, 2 H), 1.36 (s, 3 H), 0.87 (s, 9 H), 0.74 (s, 3 H), 0.00 (s, 6 H); mass spectrum m/z (relative intensity) 435 (M^+, 4), 404 (100), 378 (13), 114 (59). Anal. Calcd for $C_{25}H_{45}NO_3Si$: C, 68.91; H, 10.41; N, 3.22. Found: C, 68.70; H, 10.26; N, 3.29.

3ξ,17β-Dihydroxy-4-iodo-5-aza-4,5-seco-*B*-homoandrostan-6-one 3-*tert*-Butyldimethylsilyl Ether, 17-Benzoate (16). Epoxide **11b** (925 mg, 2.17 mmol, mixture of diastereomers) and sodium iodide (1.4 g, 9.3 mmol) were stirred in 20 mL of THF for 2 h. After evaporation of the solvent, *tert*-butyldimethylsilyl chloride (3.0 g, 20 mmol), imidazole (1.2 g, 18 mmol), and DMF (12 mL) were added, and the reaction was stirred for 48 hours. The mixture was poured into water and extracted several times with chloroform. The extract was washed repeatedly with water, dried (Na_2SO_4), evaporated, and separated by column chromatography (elution with 30% ethyl acetate–benzene) to afford 1.25 g (86%) of the iodo silyl ether **16** (mixture of diastereomers) as an oil: IR (film) 3243, 3221, 1715, 1649, 1279, 1115, 1071 cm^{-1}; ^1H-NMR δ 8.05–7.99 (m, 2 H), 7.56–7.38 (m, 3 H), 5.75 (d, J = 4.5 Hz, 1 H), 4.86 (t, J = 7.8 Hz, 1 H), 3.52 (m, 1 H), 3.14 (m, 2 H), 2.51 (m, 2 H), 1.34 and 1.33 (2 s, total 3 H), 0.96 and 0.95 (2 s, total 3 H), 0.88 (br s, 9 H), 0.06 (br s, 6 H); mass spectrum m/z (relative intensity) 667 (M^+, 3), 610 (65), 482 (70), 105 (100); exact mass calcd for $C_{28}H_{41}INO_4Si$ ($M^+ - t$-Bu): 610.1845. Found: 610.1830.

3α,17β-Dihydroxy-5-aza-*B*-homoandrostan-6-one 17-Benzoate (4) and the 3β-Isomer (5). Sodium hydride (0.96 g of a 50% dispersion in mineral oil, 20 mmol) was added cautiously to the A-seco iodo compound **16** (1.334 g, 2.000 mmol) in 60 mL of dry THF, and the mixture was stirred at room temperature for 3 h. It was then cooled to 0 °C, and 1.2 mL of acetic acid was added dropwise. The reaction mixture was poured into water and extracted several times with chloroform. The combined extracts were washed with aqueous $NaHCO_3$ and then with water, dried (Na_2SO_4), and evaporated. The residue was separated by preparative TLC on several plates (20% ethyl acetate–benzene) to afford 434 mg (40%) of the 3α-silyl ether of **4** and 374 mg (35%) of the 3β-silyl ether of **5**. The 3α-epimer had R_f 0.35: mp 117–120 °C (from hexane); IR (film) 1715, 1626, 1275, 1254, 1115 cm^{-1}; ^1H-NMR (400 MHz) δ 8.05–8.03 (m, 2 H), 7.58–7.42 (m, 3 H), 4.85 (t, J = 8.5 Hz, 1 H), 4.05 (m, w/2 = 14 Hz, 1 H), 3.78 (m, 1 H), 3.52 (m, 1 H), 2.79 (t, J = 14.0 Hz, 1 H), 2.62 (dd, J = 15.9, 6.9 Hz, 1 H), 2.31 (m, 1 H), 1.43 (s, 3 H), 0.97 (s, 3 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); mass spectrum m/z (relative intensity) 539 (M^+, 4), 524 (3), 482 (100), 105 (62); exact mass calcd for $C_{32}H_{49}NO_4Si$ 539.3431, found 539.3414. The 3β-epimer had R_f 0.58, mp 117–120 °C (from hexane): IR (film) 1715, 1626, 1277, 1107 cm^{-1}; ^1H-NMR (400 MHz) δ 8.05–8.02 (m, 2 H), 7.57–7.42 (m, 3 H), 4.89 (t, J = 8.5 Hz, 1 H), 4.26 (d, J = 13.1 Hz, 1 H), 3.65 (m, $w/2$ = 21 Hz, 1 H), 2.79 (t, J = 11.4 Hz, 1 H), 2.56 (m, 2 H), 2.30 (m, 1 H), 1.39 (s, 3 H), 0.97 (s, 3 H), 0.90 (s, 9 H), 0.10 (6 H); mass spectrum m/z (relative intensity) 539 (M^+, 3), 524 (2), 482 (100), 105 (75); exact mass calcd for $C_{32}H_{49}NO_4Si$ 539.3431, found 539.3413.

The 3α-silyl ether (220 mg, 0.408 mmol) was dissolved in 3 mL of 1 M tetra-*n*-butylammonium fluoride in THF. After 2 h, the solution was concentrated in vacuo, diluted with water, extracted several times with chloroform, dried (Na_2SO_4), and evaporated to dryness. Flash chromatography of the residue (elution with 1.5% methanol–chloroform) afforded 165 mg (95%) of the 3α-alcohol **4**, mp 243–245 °C (from ethyl acetate): IR (CCl_4) 3606, 3585, 3402, 1722, 1616, 1276, 1113 cm^{-1}; ^1H-NMR δ 8.06–8.02 (m, 2 H), 7.40–7.60 (m, 3 H), 4.89 (dd, J = 8.9 Hz, 7.8 Hz, 1 H), 4.11 (d, J = 14.2 Hz, 1 H), 4.00 (m, $w/2$ = 9 Hz, 1 H), 3.22 (d, J = 14.1 Hz, 1 H), 2.59 (m, 2 H), 1.38 (s, 3 H), 0.99 (s, 3 H); mass spectrum m/z (relative intensity) 425 (M^+, 28), 407 (5), 177 (65), 114 (87), 105 (82), 43 (100). Anal. Calcd for $C_{26}H_{35}NO_4$: C, 73.38; H, 8.29; N, 3.29. Found: C, 73.58; H, 8.21; N, 3.31.

The 3β-silyl ether was treated similarly to afford the 3β-alcohol **5** in quantitative yield, mp 256–258 °C (from ethyl acetate): IR (CCl_4) 3606, 3585, 3304, 1721, 1622, 1275 cm^{-1}; ^1H-NMR δ 8.08–8.02 (m, 2 H), 7.62–7.41 (m, 3 H), 4.89 (t, J = 8.4 Hz, 1 H), 4.00 (m, 1 H), 3.84 (m, $w/2$ = 22 Hz, 1 H), 3.28 (m, 1 H), 2.65 (m, 2 H), 1.45 (s, 3 H), 0.99 (s, 3 H); mass spectrum m/z (relative intensity) 425 (M^+, 17), 407 (5), 168 (29), 114 (92), 105 (100). Anal. Calcd for $C_{26}H_{35}NO_4$: C, 73.38; H, 8.29; N, 3.29. Found: C, 73.37; H, 8.13; N, 3.22.

Reaction of Alcohols 4 and 5 with Thionyl Chloride. The 3α-alcohol **4** (21.2 mg, 0.0499 mmol) was treated with thionyl chloride (30 mg, 0.25 mmol) in 0.5 mL of dry dichloromethane for 4 h. Volatile material was then removed in vacuo, and the residue was separated by flash chromatography (30% ethyl acetate–benzene) to afford 15.9 mg (72%) of 3α-(chloromethyl)-17β-hydroxy-5-aza-*A*-nor-*B*-homoandrostan-6-one benzoate (**21**), mp 188–190 °C (from ethyl acetate–hexane): IR (film) 1716, 1633, 1275, 1114 cm^{-1}; ^1H-NMR δ 8.08–8.02 (m, 2 H), 7.62–7.41 (m, 3 H), 4.87 (dd, J = 8.9, 7.8 Hz, 1 H), 4.54 (m, 1 H), 3.71 (dd, J = 10.4, 3.4 Hz, 1 H), 3.39 (dd, J = 10.4, 8.9 Hz, 1 H), 2.63 (m, 2 H), 1.35 (s, 3 H), 0.99 (s, 3 H); mass spectrum m/z (relative intensity) 443 (M^+, 5), 407 (59), 394 (17), 286 (23), 105 (100). Anal. Calcd for $C_{26}H_{34}ClNO_3$: C, 70.33; H, 7.72; N, 3.15. Found: C, 70.15; H, 7.67; N, 3.22.

Similarly (see Table I), the 3β-alcohol **5** afforded 63% of 3β-(chloromethyl)-17β-hydroxy-5-aza-*A*-nor-*B*-homoandrostan-6-one benzoate (**22**), mp 137–141 °C (from ethyl acetate–hexane): IR (film) 1716, 1633, 1277, 1116 cm^{-1}; ^1H-NMR δ 8.07–8.02 (m, 2 H), 7.61–7.41 (m, 3 H), 4.86 (t, J = 8.4 Hz, 1 H), 4.32 (m, 1 H), 3.89–3.80 (m, 2 H), 2.73–2.48 (m, 2 H), 1.42 (s, 3 H), 0.98 (s, 3 H); mass spectrum m/z (relative intensity) 443 (M^+, 1), 407 (100), 392 (13), 286 (22), 105 (81). Anal. Calcd for $C_{26}H_{34}ClNO_3$: C, 70.33; H, 7.72; N, 3.15. Found: C, 70.07; H, 7.72; H, 3.00. Further elution with 35% ethyl acetate–benzene afforded 14% of 3α-chloro-17β-hydroxy-5-aza-*B*-homoandrostan-6-one benzoate (**19**) with properties identical to those of the sample prepared from the reaction of **5** with triphenylphosphine and carbon tetrachloride (vide infra).

Reaction of Tosylates 17 and 18 with Lithium Chloride. The 3α-alcohol **4** (42.5 mg, 0.100 mmol) and *p*-toluenesulfonyl chloride (190 mg, 1.00 mmol) was dissolved in 1 mL of dry pyridine. After 20 h, the mixture was poured into aqueous $CuSO_4$ solution, extracted several times with chloroform, dried (Na_2SO_4), and evaporated to dryness. Flash chromatography of the residue (elution with 30% ethyl acetate-benzene) afforded 3.0 mg (7%) of the rearranged chloride[32] **21**, followed by 45.5 mg (79%) of the

(32) It is interesting that rearrangement of the tosylate **17** to **21** was noticeable even during its formation and prior to the reaction with lithium chloride. This demonstrates the facility of this process.

3α-tosylate 17. The tosylate was refluxed with 20 mol equiv of lithium chloride in 3 mL of acetone and 0.6 mL of 2-methyl-2-propanol for 8 h. The solvent was then removed under reduced pressure, and the residue was separated by preparative TLC (25% ethyl acetate–benzene) to afford 67% of the rearrangement product 21, identical to the sample from the reaction of 4 with thionyl chloride, and 22% of the substitution product 20, identical to the product obtained from the reaction of 4 with triphenylphosphine and carbon tetrachloride (vide infra).

The 3β-alcohol 5 was similarly converted to the corresponding tosylate 18 in 94% yield, without any detectable rearrangement. The reaction of 18 with lithium chloride (Table I) afforded 81% of the substitution product 19. A trace of the rearrangement product 22 was detected in the reaction mixture by TLC, but was not isolated.

Reaction of Alcohols 4 and 5 with Triphenylphosphine and Carbon Tetrachloride. A solution of the 3α-alcohol 4 (140 mg, 0.329 mmol) and triphenylphosphine (174 mg, 0.664 mmol) is dichloromethane (3 mL) and carbon tetrachloride (4 mL) was allowed to stand at room temperature for 16 h. The reaction mixture was concentrated and separated by preparative TLC (25% ethyl acetate–hexane) to afford 95 mg (65%) of 3β-chloro-17β-hydroxy-5-aza-*B*-homoandrostan-6-one benzoate (20), R_f 0.55, mp 167–168 °C (from ether–hexane): IR (film) 1717, 1630, 1277, 1119 cm^{-1}; ^{1}H-NMR δ 8.07–8.02 (m, 2 H), 7.61–7.40 (m, 3 H), 4.90 (t, J = 8.4 Hz, 1 H), 4.51 (crude d, J = 12 Hz, 1 H), 3.90 (m, $w/2$ = 26 Hz, 1 H), 3.06 (t, J = 11.9 Hz, 1 H), 2.57 (m, 2 H), 1.43 (s, 3 H), 0.99 (s, 3 H); mass spectrum, m/z (relative intensity) 443 (M$^+$ 22), 407 (62), 105 (87), 96 (100). Anal. Calcd for $C_{26}H_{34}ClNO_3$: C, 70.33; H, 7.72; N, 3.15. Found: C, 69.97; H, 7.71; N, 3.19. Also isolated were 18.9 mg (13%) of the rearranged chloride 21, R_f 0.50, identical to the sample obtained from the reaction of 4 with thionyl chloride, and 20.1 mg (15%) of 17β-hydroxy-5-aza-*B*-homoandrost-3-en-6-one benzoate (25), R_f 0.60, mp 150–153 °C (from hexane): IR (film) 1713, 1670, 1628, 1277, 1260, 1113, 914 cm^{-1}; UV λ_{max} (EtOH) 231 nm (ε = 24 000); ^{1}H-NMR δ 8.08–8.02 (m, 2 H), 7.62–7.41 (m, 3 H), 6.93 (d, J = 8.4 Hz, 1 H), 5.09 (m, 1 H), 4.88 (dd, J = 9.0, 7.7 Hz, 1 H), 2.90–2.58 (m, 2 H), 1.45 (s, 3 H), 1.00 (s, 3 H); mass spectrum m/z (relative intensity) 407 (M$^+$, 57), 105 (85), 96 (100); exact mass calcd for $C_{26}H_{33}NO_3$ 407.2460, found 407.2460.

Similarly (see Table I), the 3β-alcohol 5 afforded 88% of the substitution product 19, mp 205–208 °C (from ether–hexane): IR (film) 1715, 1628, 1277, 1116 cm^{-1}; ^{1}H-NMR (400 MHz, CD_2Cl_2, 292 K) δ 8.04–8.01 (m, 2 H), 7.59–7.43 (m, 3 H), 4.85 (t, J = 8.5 Hz, 1 H, 17α-H), 4.29 (m, 1 H, 3β-H, see also Figure 1 for variable-temperature spectra), 3.9 (br m, 2 H, 4α- and 4β-H), 2.71–2.57 (m, 2 H, 7α- and 7β-H), 1.42 (s, 3 H), 0.98 (s, 3 H); ^{1}H-NMR (400 MHz, CD_2Cl_2, 180 K) δ 4.71 (m, 17α-H and 4α-H, chair), 4.36 (m, $w/2$ = 9.5 Hz, 3β-H, chair), 4.24 (m, $w/2$ = 22.5 Hz, 3β-H, boat), 3.1–2.5 (m, 4β-, 7α- and 7β-H); mass spectrum m/z (relative intensity) 443 (M$^+$, 2), 407 (40), 392 (28), 105 (100). Anal. Calcd for $C_{26}H_{34}ClNO_3$: C, 70.33; H, 7.72; N, 3.15. Found: C, 70.58; H, 7.78; N, 3.20.

Reaction of Chlorides 19 and 20 with Aqueous Silver Nitrate. The 3α-chloride 19 (10.0 mg, 0.0226 mmol) was refluxed for 24 h in 3 mL of THF containing 0.2 mL of aqueous 0.1 M silver nitrate solution. The mixture was then concentrated, and the residue was separated by column chromatography (elution with 1.5% methanol–chloroform) to afford 7.8 mg (81%) of the rearranged alcohol 23, mp 224–227 °C (from ethyl acetate): IR ($CHCl_3$) 3397, 1713, 1596, 1280, 1118 cm^{-1}; ^{1}H-NMR δ 8.07–8.01 (m, 2 H), 7.61–7.40 (m, 3 H), 4.86 (dd, J = 9.0, 7.7 Hz, 1 H), 4.61–4.54 (m, 1 H), 3.72–3.56 (m, 2 H), 2.77–2.56 (m, 2 H), 1.38 (s, 3 H), 0.99 (s, 3 H); mass spectrum m/z (relative intensity) 425 (M$^+$, 9), 394 (100), 105 (73); exact mass calcd for $C_{26}H_{35}NO_4$ 425.2566, found 425.2539.

The 3β-chloride 20 was treated similarly for 168 h to afford 44% of the rearranged alcohol 24 and 41% of unreacted starting material. The product 24 had mp 178–182 °C (from ethyl acetate): IR ($CHCl_3$) 3367, 1713, 1602, 1280, 1119 cm^{-1}; ^{1}H-NMR δ 8.06–8.01 (m, 2 H), 7.62–7.40 (m, 3 H), 4.87 (dd, J = 9.0, 7.8 Hz, 1 H), 4.24–4.11 (m, 1 H), 3.86–3.55 (m, 2 H), 2.75–2.53 (m, 2 H), 1.39 (s, 3 H), 0.98 (s, 3 H); mass spectrum, m/z (relative intensity) 425 (M$^+$, 7), 394 (79), 105 (91), 40 (100); exact mass calcd for $C_{26}H_{35}NO_4$ 425.2566, found 425.2569.

3α-(Chloromethyl)-17β-hydroxy-5-aza-*A*-nor-*B*-homoandrostan-6-one *tert*-Butyldimethylsilyl Ether (35) and the 3β-Isomer (36). Alcohol 12 (29.5 mg, 0.0678 mmol) and 12 μL (0.16 mmol) of thionyl chloride were stirred in 1 mL of dry dichloromethane for 3 h. The mixture was then concentrated and flash chromatographed (elution with 50% ethyl acetate–hexane) to give 30.8 mg (100%) of the crude product. Recrystallization from hexane afforded 22.7 mg (76%) of the 3α-chloromethyl derivative 35, mp 167–168 °C: IR (film) 1633, 1141, 1088, 835 cm^{-1}; ^{1}H-NMR δ 4.53 (m, 1 H), 3.70 (dd, J = 10.3, 3.4 Hz, 1 H), 3.56 (t, J = 8.2 Hz, 1 H), 3.37 (dd, J = 10.3, 8.8 Hz, 1 H), 2.61 (m, 2 H), 1.32 (s, 3 H), 0.88 (s, 9 H), 0.74 (s, 3 H), 0.01 (s, 6 H); mass spectrum m/z (relative intensity) 453 (M$^+$, 9), 417 (78), 402 (95), 396 (50), 132 (85), 75 (100). Anal. Calcd for $C_{25}H_{44}ClNO_2Si$: C, 66.11; H, 9.77; N, 3.08. Found: C, 66.02; H, 9.76; N, 3.04.

Similarly, alcohol 13 afforded 56% of the recrystallized 3β-chloromethyl isomer 36, mp 145–146 °C (from hexane): IR (film) 1633, 1137, 1095, 835 cm^{-1}; ^{1}H-NMR δ 4.32 (m, 1 H), 3.83 (d, J = 4.8 Hz, 2 H), 3.56 (t, J = 8.1 Hz, 1 H), 2.65–2.38 (m, 2 H), 1.39 (s, 3 H), 0.88 (s, 9 H), 0.74 (s, 3 H), 0.01 (s, 6 H); mass spectrum m/z (relative intensity) 453 (M$^+$, 5), 417 (100), 402 (29), 360 (30). Anal. Calcd for $C_{25}H_{44}ClNO_2Si$: C, 66.11; H, 9.77; N, 3.08. Found: C, 65.77; H, 9.81; N, 3.41.

Solvolyses of Chlorides 19, 20, 30, 31, and 32 (General Procedure). All of the solvolyses were performed under identical conditions: The chloride (ca. 20 mg) was refluxed in 6 mL of a stock solution prepared from 480 mg of silver nitrate, 36.0 mL of THF, and 2.4 mL of water. When TLC and NMR analysis indicated that the reaction had proceeded substantially, the solvent was removed and the remaining starting material was isolated by column chromatography. The percent conversion (100% − % of recovered starting material) and the time required were as follows: 19, 32% at 0.5 h; 20, 27% at 96 h; 30, 67% at 18 h; 31, 15% at 159 h; 32, 57% at 2 h.[33]

X-ray Crystallography of Chloroazasteroids 19, 20, 21, and 36. Compound 19. Transparent, colorless single crystals of 19 were grown by slow evaporation of a dichloromethane/hexane solution. A crystal of dimensions 0.11 × 0.11 × 0.36 mm was used for data collection with an Enraf Nonius CAD-4F diffractometer, Ni-filtered CuK_α radiation (λ = 1.541 78 Å), and $\omega/2\theta$ scans. The crystal system is orthorhombic, space group $P2_12_12_1$, a = 6.2213 (3) Å, b = 11.8309 (5) Å, c = 31.8184 (9) Å, V = 2341.9 (2) Å^3, Z = 4, density (calcd) = 1.259 g cm^{-3}, and μ = 16.5 cm^{-1}. Two octants of data were collected to a maximum θ of 75°; of 6017 reflections measured, the 5577 replicative data were averaged (R_{int} = 0.026) to obtain 2790 unique reflections; of these 2554 had $I > 2.5\sigma(I)$ and were treated as observed. The structure was solved by direct methods with the program SHELXS86[34] and was refined on F's with the program XRAY76.[35] All H atoms were found in difference Fourier syntheses. The final cycles of blocked least-squares varied 417 variables: the positions of all atoms, the anisotropic thermal parameters of the non-H atoms, the isotropic thermal parameters of the H atoms, the scale factor, and the isotropic extinction parameter (final value 4.67 (9) × 10^{-3}). The refinement converged with a maximum shift/error of 0.037, R = 0.035, R_w = 0.034 ($\omega^{-1} = \sigma_F^2 + 0.000\,025|F|^2$) and S = 1.09 for the 2554 observed reflections.

Compound 20. Transparent, colorless single crystals of 20 were grown by slow evaporation of a dichloromethane/ethanol solution. A crystal of dimensions 0.18 × 0.26 × 0.40 mm was used for data collection via the procedure for 19. The crystal system is monoclinic, space group $P2_1$, a = 10.2746 (7) Å, b = 13.7504 (6)

(33) These results are not intended to convey precise kinetic information about the solvolyses of compounds 19, 20, 30, 31, and 32, but suffice to illustrate their widely differing relative reactivities under the conditions employed. If it is assumed that the solvolyses of these compounds obey first-order kinetics, then their respective half-lives ($\tau_{1/2}$) would be 1, 200, 10, 700, and 2 h.

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(35) Steward, J. M. *The XRAY76 System of Crystallographic Programs*; Computer Science Center, University of Maryland: College Park, Maryland, 1976.

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Å, c = 16.9919 (4) Å, β = 94.701 (3)°, V = 2392.5 (2) Å^3, Z = 4, density (calcd) = 1.233 g cm^{-3}, and μ = 16.2 cm^{-1}. One quadrant of data was collected to a maximum θ of 75°; of 5677 reflections measured, there were 5118 unique reflections; of these, 4504 had $I > 2.5\sigma(I)$ and were treated as observed. The structure was solved and refined as for **19**. All H atoms were found in difference Fourier syntheses. The final cycles of blocked least-squares varied 831 variables: the positions of all atoms, the anisotropic thermal parameters of the non-H atoms, the isotropic thermal parameters of the H atoms, the scale factor, and the isotropic extinction parameter (final value 5.97 (12) × 10^{-3}). The refinement converged with a maximum shift/error of 0.040, R = 0.040, R_w = 0.044 ($w^{-1} = \sigma_F^2 + 0.0001|F|^2$) and S = 1.06 for the 4504 observed reflections.

Compound **21**. Transparent, colorless single crystals of **21** were grown by slow evaporation of a dichloromethane/methanol solution. A crystal of dimensions 0.22 × 0.36 × 0.44 mm was used for data collection via the procedure for **19**. The crystal system is monoclinic, space group $P2_1$, a = 10.0032 (10) Å, b = 7.2060 (7) Å, c = 16.9019 (13) Å, β = 101.293 (7)°, V = 1194.8 (2) Å^3, Z = 2, F(000) = 476, density (calcd) = 1.234 g cm^{-3}, and μ = 16.2 cm^{-1}. One quadrant of data was collected to a maximum θ of 75°; of 3016 reflections measured, there were 2652 unique reflections; of these 2300 had $I > 2.5\sigma(I)$ and were treated as observed. The structure was solved and refined as for **19**. Most of the H atoms were found in difference Fourier syntheses, and positions of the missing H atoms were calculated based on idealized geometry. The final cycles of blocked least-squares varied 356 variables: the positions and the anisotropic thermal parameters of the non-H atoms, the positions and the isotropic thermal parameters of some H atoms, the scale factor, and the isotropic extinction parameter (final value 1.82 (16) × 10^{-3}). The remaining H atoms were included in the refinement with fixed positions and with U_{iso} equal to 120% of the U_{eq} of the carbon atoms to which they are attached. The refinement converged with a maximum shift/error of 0.004, R = 0.055, R_w = 0.067 ($w^{-1} = \sigma_F^2 + 0.0003|F|^2$) and S = 1.13 for the 2300 observed reflections.

Compound **36**. Transparent, colorless single crystals of **36** were grown by slow evaporation of a dichloromethane/methanol solution. A crystal of dimensions 0.06 × 0.26 × 0.48 mm was used for data collection via the procedure for **19**. The crystal system is monoclinic, space group $P2_1$, a = 7.609 (1) Å, b = 9.236 (1) Å, c = 19.060 (5) Å, β = 100.83 (2)°, V = 1315.6 (4) Å^3, Z = 2, density (calcd) = 1.146 g cm^{-3}, and μ = 18.8 cm^{-1}. One quadrant of data was collected to a maximum θ of 60°; of 2461 reflections measured, there were 2098 unique reflections; of these 1353 had $I > 2.5\sigma(I)$ and were treated as observed. The structure was solved and refined as for **19**. Atoms C(1) and C(2) of the A ring were disordered; the two positions of each of these atoms, C(1′) and C(1″), and C(2′), and C(2″), were found in the difference Fourier map. Positions of H atoms were calculated. The final cycles of blocked least-squares varied 268 variables: the positions and the anisotropic thermal parameters of the non-H atoms except atoms C(1′), C(1″), C(2′), and C(2″), which were refined with isotropic thermal parameters and occupancy factors of 50%, and the scale factor. All H atoms were included in the refinement with fixed positions and with U_{iso} equal to 120% of the U_{eq} of the carbon atoms to which they are attached. The refinement converged with a maximum shift/error of 0.009, R = 0.079, R_w = 0.086 ($w^{-1} = \sigma_F^2 + 0.0004|F|^2$) and S = 1.03 for the 1353 observed reflections.

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Supplementary Material Available: Tables of coordinates, thermal parameters, bond distances, bond angles, and endocyclic plus other selected torsional angles for the X-ray structure determinations of **19**, **20**, **21**, and **36** and REFCODES and detailed geometry of other 7-membered lactams (44 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.