Approximate interproton distances (Table II) found for the model structures provide further information to clarify the structure of moroidin. While all model structures discussed are necessarily static representations of dynamic systems, the positions of the individual atoms should be indicative of "average" internuclear separations and thus should correlate with proton-proton NOEs. As concluded earlier, structures **1b** and **1d** are inconsistent with the experimental data presented herein, and this is highlighted again by the data in Table II. Neither structure would be expected to exhibit NOEs between the proton pairs Trp_{C_5}-$\beta^S Leu_{\alpha CH}$ and $Trp_{\beta CH}$-His_{C_5} (and in **1d**, $His_{\alpha CH}$-His_{C_4}), contrary to the experimental findings.

The distinction between structures **1a** and **1c** is apparent upon examination of their three-dimensional structure and is also revealed by the measured interproton distances in Table II. Topologically, the two structures are essentially identical over the "western" peptide ring containing the pyroGlu-β^SLeu-Leu-Val-Trp residues. They differ dramatically, however, over the "eastern" peptide ring formed by the Arg-Gly-His-Trp residues. These differences are no doubt a consequence of the $indole_{Trp}$-$imidazole_{His}$ attachment, although it is interesting that a change in this linkage affects only the conformation of the ring in which it is contained-no effect is observed in the ring containing the Val-Leu-pyroGlu-β^SLeu residues. In the case of **1c**, this conformational change causes the Trp_{C_β} and His_{C_5} protons to become separated by more than 4.0 Å, a distance inconsistent with the strong NOE found between these protons. Furthermore, **1c** does not account for the NOE observed between Gly_{NH} and Arg_{NH}, although here molecular dynamics simulations indicate that the flexibility in the eastern ring could possibly result in a flip of the Gly_{NH} amide linkage allowing the closer approach of Gly_{NH} and Arg_{NH} in model structure **1c**. In **1a**, Gly_{NH} bisects the plane spanned by the Arg_{NH} and C_α protons, in accord with the observed NOE to both these atoms.

Consideration of the NOE and coupling constant data, in conjunction with the molecular modeling studies, leads to the conclusion that moroidin possesses structure **1a**. Negative evidence consistent with the conclusion is the absence of any NOE between His_β and Trp_β, which in structure **1c** would be expected to be large, but is not predicted in structure **1a**.

In order to test the validity of the calculations on structure **1a**, this form was also energy minimized by using the CHARMM force field.[22] The results obtained were entirely compatible with those found by using the COSMIC force field, confirming that the result was not dependent on the particular force field used.

Conclusions

Using a combination of NMR and molecular modeling techniques, the structure of moroidin is shown to be composed entirely of L amino acids. Consideration of scalar proton-proton coupling constants eliminates structures having an *R* configuration at either the β-substituted leucine or tryptophan residues. Intramolecular NOEs further define the linkage between C_2 on the tryptophan indole and N_1 on the imidazole ring of histidine. Structure **1a** therefore represents the correct structure of moroidin. Molecular modeling via molecular mechanics and molecular dynamics using the COSMIC force field has been shown to be a highly efficient means of correlating available experimental data with several possible structural variations of moroidin.

Acknowledgment. Discussions, technical support, and computer time, provided by the Molecular Graphics Research staff of Smith, Kline, and French (Welwyn, England), are gratefully acknowledged, as is an additional sample of crude moroidin extract provided by Dr. P. B. Oelrichs (Animal Research Institute, Queensland, Australia). We thank Merck (U.K.) for financial support, and S.D.K. thanks Churchill College for a Fellowship during his tenure at Cambridge.

Registry No. 1, 104041-75-0; **1a**, 119528-95-9; **1b**, 119616-50-1; **1c**, 119528-96-0; **1d**, 119616-51-2.

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N-Chloroazasteroids: A Novel Class of Reactive Steroid Analogues. Preparation, Reaction with Thiols, and Photochemical Conversion to Electrophilic *N*-Acyl Imines

Thomas G. Back* and Kurt Brunner

Department of Chemistry, University of Calgary, Calgary, Alberta, Canada T2N 1N4

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N-Chloroazasteroids **2**, **5**, **7**, **10**, **12**, **15**, **18**, and **22** were easily prepared by the reaction of *N*-chlorosuccinimide with the parent azasteroid lactams **1**, **4**, **6**, **9**, **11**, **14**, **17**, and **21**, respectively. The products reacted with the model thiols benzenethiol and L-cysteine ethyl ester to afford the corresponding *N*-thiolactams **3**, **8**, **13**, **16**, and **23**, as well as the parent lactams and disulfides, via sulfenyl chloride intermediates. The reaction of benzenethiol with *N*-chloro-17β-hydroxy-4-aza-3-androstanone (**2**) resulted in the anomalous formation of the stable sulfenate and sulfinate esters **24a** and **24b**. Photolyses of *N*-chloroazasteroids in methanol resulted in the formation of enamides **27**, **28**, and **30**, or the carbinol amide methyl ethers **32** and **34**. These products were formed by the isomerization or solvent trapping of reactive *N*-acyl imine intermediates. The ability of *N*-chloroazasteroids to react covalently with thiols and to generate electrophilic *N*-acyl imines suggests potential biological applications in affinity labeling and enzyme inhibition and for use as antihormonal agents.

Steroid analogues that contain alkylating or other reactive functional groups have several potentially useful applications. When such species mimic natural steroid hormones with respect to recognition by their respective

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Table I. Preparation of N-Chloroazasteroids

lactam	method[a]	N-chloroazasteroid	% yield[b]
1	A	2	86
4	B	5	90
6	A	7	83
9	A	10	80
11	B	12	85
14	B	15	75
17	C	18	73
21	B	22	70

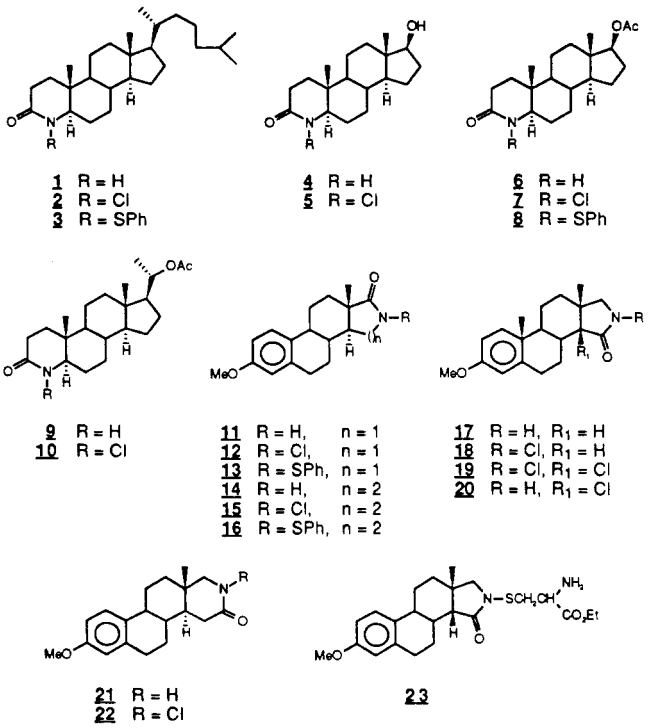
[a] Method A: NCS, refluxing $CHCl_3$. Method B: (1) KO-t-Bu, THF; (2) NCS, THF, room temperature. Method C: (1) KO-t-Bu, THF; (2) NCS, THF, slow addition, room temperature. [b] Isolated yields are reported.

protein receptors, irreversible covalent bonding can occur between the modified steroid and complementary functional groups within the active site. Such compounds have been successfully employed in affinity-labeling studies of steroid receptors.[1,2]

Second, enzymes that normally transform steroid substrates may react irreversibly with reactive mimics of the latter. This can be exploited in the design of enzyme inhibitors that have medicinally useful properties stemming from their ability to block the biosynthesis of physiologically undesirable steroids further along the biosynthetic pathway.[3,4]

Third, steroids containing cytotoxic alkylating groups have been employed in the treatment of cancers of tissues that are rich in steroid receptors. Thus, steroids with appended nitrogen-mustard side chains (the "estramustines") have been used in the chemotherapy of breast and prostate tumours.[5] Enhanced selectivity for the target tissue and decreased systemic toxicity is envisaged from the incorporation of the cytotoxic group directly into the steroid nucleus, rather than in an appended unnatural side chain, which presumably perturbs the recognition process.

Chart I



It has been reported that thiol (sulfhydryl) groups play a crucial role in the binding of certain natural steroid hormones such as estradiol.[6] Consequently, reactive steroid mimics displaying chemoselectivity for thiol groups[2d,g] are of special significance.

We now report the preparation of several novel N-chloroazasteroids from azasteroid lactam precursors in the cholestane, androstane, pregnane, and estrane series and describe their reactions with some model thiols.[7] In addition, we report that N-chloroazasteroids can function as precursors of highly reactive, electrophilic N-acyl imines.

Results and Discussion

Preparation of N-Chloroazasteroids. The required azasteroid lactams 1,[8] 4,[9] 6,[9] 9,[9] 11,[10] 14,[11] 17,[11] and 21[11] (Chart I) were obtained by methods described previously. They were converted to the desired N-chloro derivatives either by refluxing in chloroform with excess N-chlorosuccinimide (NCS) or by their reaction with potassium *tert*-butoxide followed by NCS in THF at room temper-

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(5) For reviews, see: (a) Leclercq, G.; Heuson, J. C. *Curr. Prob. Cancer* **1976**, *1*, 1. (b) Hamacher, H.; Bormann, B.; Christ, E. In *Cytotoxic Estrogens in Hormone Receptive Tumours*; Raus, J., Martens, H., Leclercq, G., Eds.; Academic Press: New York, 1980; pp 107–122. (c) Sandberg, A. A. In *Vitamins and Hormones*; Munson, P. L., Diczfalusy, E., Glover, J., Olson, R. E., Eds.; Academic Press: New York, 1975; Vol. 33, pp 155–188. (d) Jonsson, G.; Olsson, A. M.; Luttrop, W.; Cekan, Z.; Purvis, K.; Diczfalusy, E. in ref 5c, pp 351–376.

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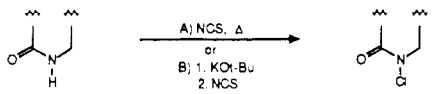
(11) Back, T. G.; Brunner, K. *Heterocycles*, in press.

ature (eq 1). The yields of the respective products **2**, **5**, **7**, **10**, **12**, **15**, **18**, and **22** (Chart I) are shown in Table I.



(1)

In the case of the conversion of azasteroid **17** to the *N*-chloro compound **18**, chlorination also occurred at the 14-position to produce **19** as a byproduct (and **20** after reaction with benzenethiol). Moreover, we observed in a separate experiment that the *N*-chloroazasteroid **18** isomerizes to the 14-chloro derivative **20** in the presence of excess potassium *tert*-butoxide. These side reactions presumably proceed via chlorination of the enolate of **18** by NCS or by **18** itself, respectively. They were effectively suppressed by the slow addition of NCS to an equimolar mixture of **17** and potassium *tert*-butoxide.

Chlorination with sodium or *tert*-butyl hypochlorite was also attempted in several cases but gave inferior results.

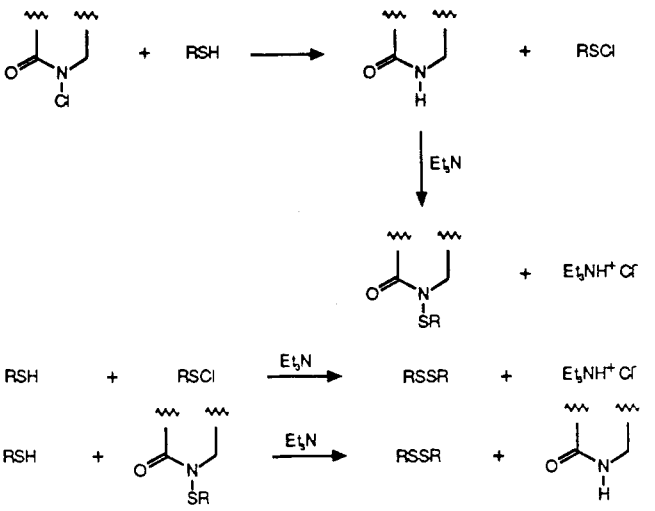
The *N*-chloroazasteroids proved to be stable, crystalline solids that could be chromatographed on silica gel without decomposition and stored indefinitely at 0 °C in the dark. Some decomposition was evident, however, upon extensive exposure to bright light. The *N*-chloroazasteroids were also recovered intact when dissolved for 24 h in ethanol–water mixtures. Their stability in aqueous media is, of course, a prerequisite for applications in vivo.

Reactions of *N*-Chloroazasteroids with Thiols. The reactions of *N*-chloro imides such as NCS with thiols are known to afford *N*-thio imides.[12] We therefore attempted to determine whether the *N*-chloroazasteroids in Table I would react similarly with a model thiol, as such behavior would be a positive indication of their ability to form covalent S–N bonds with thiol groups in steroid receptors.

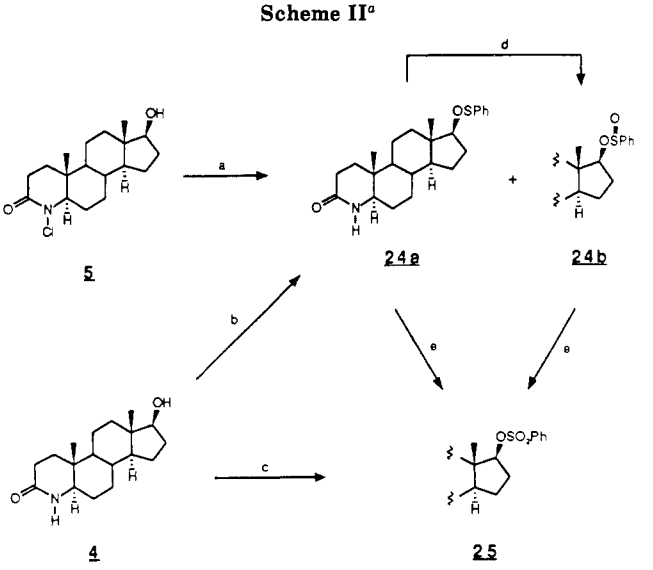
Admixture of benzenethiol with *N*-chloroazasteroids **2**, **7**, **12**, and **15** in either chloroform or THF resulted in the rapid appearance of the characteristic yellow-orange color of benzenesulfenyl chloride (PhSCl). When triethylamine was added to the solution, the color rapidly disappeared to afford the corresponding *N*-thiolactams **3**, **8**, **13**, and **16** in yields of 31, 33, 16, and 32%, respectively. Omission of triethylamine resulted in a slower reaction, as evidenced by a more gradual disappearance of the color. The formation of the parent lactams and diphenyl disulfide accompanied that of the *N*-thiolactams in each case, accounting for nearly all of the remaining mass balance. Similarly, *N*-chloroazasteroid **17** reacted with L-cysteine ethyl ester hydrochloride to produce the *N*-thiolactam derivative **23**, albeit in low yield. Again, the disulfide and the parent lactam comprised the major byproducts. The *N*-thiolactams proved to be stable, homogeneous (TLC), amorphous gums or solid foams, except for product **13**, which was a crystalline solid.

A plausible mechanism for these transformations is shown in Scheme I. Chlorination of the thiol by the *N*-chloro compound presumably occurs in a similar manner to the known reaction of thiols with NCS[12,13] and is followed by the N-sulfenylation of the resulting lactam by the sulfenyl chloride.[14] The formation of the lactam and disulfide byproducts most probably results from the competing reaction of the thiol with the sulfenyl chloride or with the product *N*-thiolactam. The reaction of thiols with

Scheme I



Scheme II[a]



[a] (a) PhSH, Et_3N; (b) PhSCl, Et_3N; (c) $PhSO_2Cl$, Py, DMAP; (d) MCPBA, 1 equiv; (e) MCPBA, excess.

sulfenyl chlorides is known[15] and that with *N*-thiolactams was confirmed by a control experiment in which the *N*-thiolactam **16** was observed to react rapidly with benzenethiol under similar conditions in the presence of triethylamine, to produce the lactam **14** and diphenyl disulfide.[16]

It is worth noting that more efficient *N*-thiolactam formation would be expected in the highly ordered environment of an active site. Since competing disulfide formation requires the presence of a second mole of the thiol to react with either the sulfenyl chloride or the *N*-thiolactam, this process would have a far lower probability in vivo than in the model experiments described here. Disulfide formation under such circumstances would only be expected if two thiol residues existed in close proximity to each other in the active site and to the *N*-chloro moiety of the complexed steroid.

Anomalous Formation of Sulfenate and Sulfinate Esters from *N*-Chloroazasteroid 5. The reaction of

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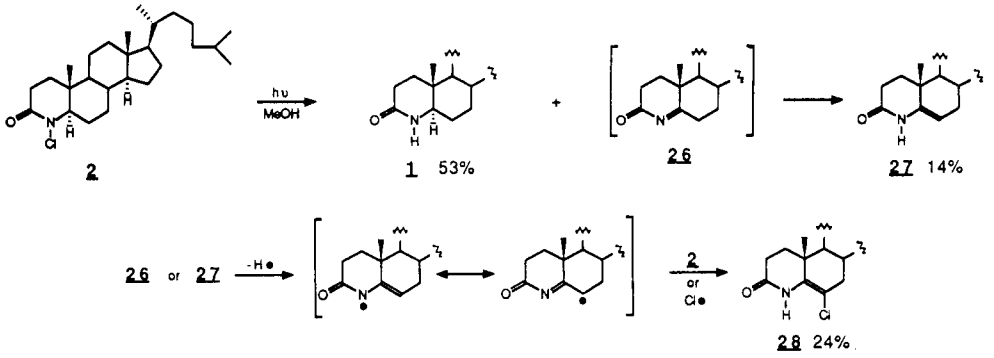
(13) Emde, H. German Patent 804,572 (1951); *Chem. Abstr.* **1952**, *46*, 529.
(14) (a) Kittleson, A. R. U.S. Patent 2,553,770 (1951); *Chem. Abstr.* **1951**, *45*, 6791. (b) Behforouz, M.; Kerwood, J. E. *J. Org. Chem.* **1969**, *34*, 51.
(15) Douglass, I. B.; Martin, F. T.; Addor, R. *J. Org. Chem.* **1951**, *16*, 1297.
(16) Thiols are known to react in this fashion with the related *N*-thio imides: (a) Boustany, K. S.; Sullivan, A. B. *Tetrahedron Lett.* **1970**, 3547. (b) Harpp, D. N.; Ash, D. K.; Back, T. G.; Gleason, J. G.; Orwig, B. A.; VonHorn, W. F.; Snyder, J. P. *Tetrahedron Lett.* **1970**, 3551.

Scheme III



N-chloroazasteroid **5** with benzenethiol under the usual conditions did not afford the expected N-thiolactam. Instead, a mixture of the sulfenate and sulfinate esters **24a** and **24b** (Scheme II), respectively, was obtained in ca. 23% yield, along with the parent lactam **4** and diphenyl disulfide. Although the relative proportions of **24a** and **24b** varied with the exact conditions, the sulfinate ester **24b** comprised the chief product. It was formed as a mixture of two diastereomers resulting from the chiral sulfinate sulfur atom, and one of these isomers could be isolated in a pure state by recrystallization.[17] The same products **24a** and **24b** were produced when the parent lactam **4** was treated with authentic benzenesulfenyl chloride followed by triethylamine. The sulfenate ester **24a** was the principal product when 1.5 molar equiv of the sulfenyl chloride were employed and the triethylamine was added with little delay. It was isolated in up to 43% yield as a remarkably stable, crystalline solid. Its stability was unexpected as only a few sulfenates have been isolated to date, with most being relatively susceptible to hydrolysis and disproportionation.[18] The use of greater excesses of the sulfenyl chloride and longer delays prior to the introduction of the triethylamine resulted in the formation of larger quantities of **24b**, as well as N-sulfenylated products that were not further characterized.

The structures of products **24a** and **24b** were confirmed by their chemical behavior, as well as from spectroscopic and analytical data. When sulfenate ester **24a** was oxidized with 1 equiv of *m*-chloroperbenzoic acid (MCPBA), it afforded the same mixture of diastereomers of the sulfinate ester **24b**, along with a small amount of the corresponding sulfonate ester **25**. The oxidation of either sulfenate **24a** or sulfinate **24b** with excess MCPBA produced only sulfonate **25**, which was identical with a sample prepared from the reaction of the parent lactam **4** with benzenesulfonyl chloride. These transformations are summarized in Scheme II.

Compounds **24a**, **24b**, and **25** all showed IR absorptions in the region 3395–3397 cm^{-1} (dilute $CHCl_3$) and broad singlets in their ^1H NMR spectra at δ 5.86–5.41, attributed to the lactam NH moiety. Moreover, the ^1H NMR signal from the proton at C-17 was shifted progressively further downfield with increasing oxidation state of the sulfur atom relative to lactam **4** (δ 3.69 for **24a**, δ 4.17 and 4.08 for the two diastereomers of **24b**, and δ 4.29 for **25** vs δ 3.64 for **4**), whereas the resonance from the proton at C-5 remained virtually unchanged in all of these compounds (δ 3.02–3.05). This confirms that sulfenylation occurred at the C-17 hydroxyl group and not at the lactam nitrogen atom.

Whereas the formation of the sulfenate ester **24a** occurs by direct sulfenylation of the azasteroid by the sulfenyl chloride, that of the sulfinate ester **24b** requires an additional oxidation step. Sulfenyl chlorides are known to transform sulfenates to sulfinates,[18c] and presumably a similar process operates here. The observation that the treatment of azasteroid **4** with a large excess of benzenesulfenyl chloride for longer times produces increased quantities of **24b** is consistent with this explanation.

***N*-Acyl Imines from Photolyses of *N*-Chloroazasteroids.** Azasteroidal N-acyl imines comprise another potentially useful class of reactive analogues of steroid hormones. If the electrophilic N-acyl imine functionality could be delivered to, or generated in, the active site of a receptor, then irreversible reaction with nucleophilic groups in the latter would be expected. Previous attempts to prepare such species by oxidation of the parent lactams with benzeneseleninic anhydride have been reported,[9,19] but further reactions generally prevented their isolation. In some instances the corresponding hydrates (carbinol amides) were obtained in high yield.[19] Since the desired N-acyl imines are formally the products of dehydrohalogenation of the N-chloroazasteroids, we investigated methods for effecting this transformation.

The direct dehydrohalogenation of N-chloroazasteroids with a variety of bases, including lithium carbonate, DBU and DBN, potassium *tert*-butoxide, and several amines and lithium amides, was attempted but failed to give satisfactory results. However, it has been reported that N-chloroamines[20] and N-chloro-N-methyl amides[21] undergo free-radical dehydrohalogenation to produce the corresponding aldimines and N-acyl imines when treated with silver, or when subjected to photolysis, respectively. We therefore investigated the photolysis of several of the above N-chloroazasteroids to ascertain whether parallel behavior would be observed. The photochemical generation of N-acyl imines from N-chloroazasteroids would make them of potential interest as photoaffinity-labeling agents.[22]

Photolyses performed in benzene or carbon tetrachloride afforded the parent lactams as well as complex mixtures of other products, which were not further studied. How-

(17) The physical and spectral characteristics of this sulfinate ester diastereomer **24b** were erroneously attributed to the sulfenate ester **24a** in our preliminary communication (ref 7).

(18) (a) Letsinger, R. L.; Fontaine, J.; Mahadevan, V.; Schexnayder, D. A.; Leone, R. E. *J. Org. Chem.* **1964**, *29*, 2615. (b) Barton, D. H. R.; Page, G.; Widdowson, D. A. *J. Chem. Soc., Chem. Commun.* **1970**, 1466. (c) Moore, T. L.; O'Connor, D. E. *J. Org. Chem.* **1966**, *31*, 3587.

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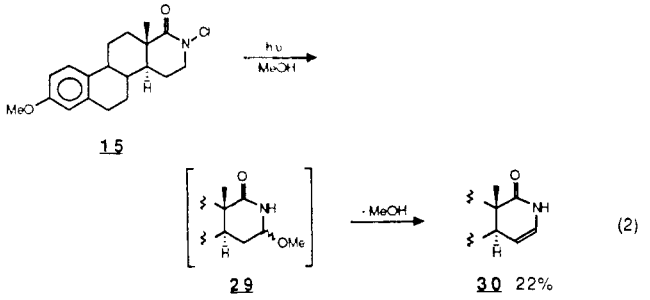
(20) (a) Edwards, O. E.; Vocelle, D.; ApSimon, J. W. *Can. J. Chem.* **1972**, *50*, 1167. (b) Edwards, O. E.; Paskovich, D. H.; Reddoch, A. H. *Can. J. Chem.* **1973**, *51*, 978.

(21) Neale, R. S.; Marcus, N. L.; Schepers, R. G. *J. Am. Chem. Soc.* **1966**, *88*, 3051.

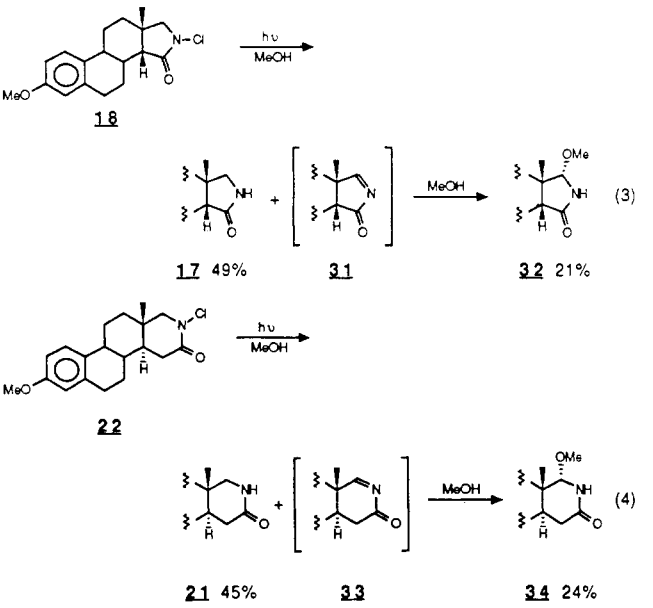
(22) For examples of photoaffinity labeling of steroid receptors with diazo compounds and azides, see: (a) Katzenellenbogen, J. A.; Myers, H. N.; Johnson, H. J., Jr. *J. Org. Chem.* **1973**, *38*, 3525. (b) Katzenellenbogen, J. A.; Johnson, H. J., Jr.; Myers, H. N. *Biochemistry* **1973**, *12*, 4085.

ever, when the *N*-chloroazasteroid **2** was photolyzed in methanol, the products included the enamide **27** and its 6-chloro derivative **28** along with lactam **1** (Scheme III). These results suggest the intermediacy of the *N*-acyl imine **26**, presumably formed by the homolytic cleavage of the N–Cl bond of **2**, followed by disproportionation of the nitrogen-centered radicals, or by hydrogen abstraction from C-5 of the latter by the chlorine atom. Isomerization of **26** then afforded the more stable enamide **27**, and free-radical chlorination of either **26** or **27** produced **28**.[23]

The photolysis of *N*-chloroazasteroid **15** furnished the enamide **30** as shown in eq 2. HPLC analysis of the reaction mixture detected a pair of poorly resolved intermediates, which were too unstable to isolate and which were probably the α and β isomers of the carbinol amide methyl ether **29**, formed by solvent trapping of the corresponding *N*-acyl imine intermediate. Loss of methanol from **29** is expected to produce enamide **30** instead of the less stable *N*-acyl imine isomer.



We also investigated the photolysis of the *N*-chloroazasteroids **18** and **22**, where isomerization of the expected *N*-acyl imines **31** and **33** to enamides is precluded by the presence of the quaternary carbon atoms at C-13. Solvent addition should consequently be the favored pathway if the *N*-acyl imines are produced. As anticipated, the principal products, apart from the parent lactams, were the 17- and 17a-methoxy derivatives **32** and **34**, respectively[24] (eq 3 and 4). Their formation confirms the intermediacy of highly reactive, electrophilic *N*-acyl imines in the photolyses of these *N*-chloroazasteroids.



Conclusions

N-Chloroazasteroids are easily prepared by the chlorination of their parent lactams with NCS. They are stable in protic solvents but react readily with thiols to form *N*-thiolactams (or in one case sulfenate and sulfinate esters). These model experiments suggest that such compounds would bond covalently to thiol groups in steroid receptors or in enzymes that recognize them as substrates.

Photolyses of *N*-chloroazasteroids generate reactive *N*-acyl imines, which rapidly isomerize to enamides or undergo addition of solvent. Possible applications as photoaffinity labeling agents are suggested by this behavior.

Experimental Section

Melting points were determined on an A. H. Thomas hot-stage apparatus and are uncorrected. IR spectra were recorded on a Nicolet 5DX spectrometer, with KBr disks for solid samples and neat films for oils, unless otherwise noted. ^{1}H and ^{13}C NMR spectra were obtained at 200 MHz with a Varian XL200 or a Bruker AC-E 200 spectrometer, with deuteriochloroform as the solvent and either chloroform or tetramethylsilane as the internal standard. High- and low-resolution mass spectra were recorded on a Kratos MS80 or a VG 7070 spectrometer. Optical rotations were measured on a Rudolph Autopol III polarimeter in chloroform solution unless otherwise indicated. Preparative TLC was carried out on Analtech 20 × 20 cm glass plates coated with 1 mm of silica gel GF. HPLC separations were carried out on a Varian VISTA 5060 apparatus equipped with a UV-100 detector and a Varian Micropak MCH-10 column (50 cm × 8 mm), using 25% water–methanol as the solvent under isocratic conditions. Photolyses were carried out in a Rayonet RMR-500 reactor equipped with four 254-nm lamps. Elemental analyses were obtained by Dr. W. S. Lin (University of Calgary). THF and methanol were freshly distilled from lithium aluminum hydride and magnesium metal, respectively, prior to use. MCPBA was purified by a literature procedure[25] and was assumed to be 100% pure. Benzenesulfenyl chloride was prepared by treating diphenyl disulfide with an equimolar amount of freshly redistilled sulfuryl chloride[26] in chloroform solution for 30 min.

Preparation of *N*-Chloroazasteroids (See Table I). Method A: *N*-Chloro-4-aza-3-cholestanone (2) (Typical Procedure). Lactam **1** (104 mg, 0.27 mmol) and NCS (200 mg, 1.50 mmol) were refluxed 25 h in 10 mL of chloroform. The mixture was separated by preparative TLC in 50% ether–hexane to afford 98 mg (86%) of the title compound: R_f 0.35; mp 149–151 °C (from dichloromethane–methanol); $[\alpha]_D$ +14° (*c* 0.36); IR 1697, 1505, 1282, 1218 cm^{-1}; ^{1}H NMR δ 3.31 (dd, J = 12.4, 3.6 Hz, 1 H), 2.66 (m, 2 H), 0.99 (s, 3 H), 0.90 and 0.86 (2 overlapping d, 9 H total), 0.67 (s, 3 H). Anal. Calcd for $C_{26}H_{44}ClNO$: C, 73.97; H, 10.51; N, 3.32. Found: C, 74.10; H, 10.29; N, 3.27.

Similarly prepared were the following:

***N*-Chloro-17β-acetoxy-4-aza-3-androstanone (7)**: mp 250 °C dec (from dichloromethane–hexane); $[\alpha]_D$ −19° (*c* 1.525); IR ($CHCl_3$) 1724, 1664, 1258, 1034 cm^{-1}; ^{1}H NMR δ 4.60 (t, J = 7.5 Hz, 1 H), 3.32 (dd, J = 12.4, 3.5 Hz, 1 H), 2.66 (m, 2 H), 2.04 (s, 3 H), 1.00 (s, 3 H), 0.80 (s, 3 H). Anal. Calcd for $C_{20}H_{30}ClNO_3$: C, 65.29; H, 8.22; N, 3.81. Found: C, 65.09; H, 8.25; N, 3.60.

***N*-Chloro-20-acetoxy-4-aza-3-pregnanone (10)**: mp 141–143 °C dec (from dichloromethane–hexane); $[\alpha]_D$ +35° (*c* 0.625); IR 1726, 1692, 1673, 1246 cm^{-1}; ^{1}H NMR δ 4.84 (m, 1 H), 3.31 (dd, J = 12.5, 3.5 Hz, 1 H), 2.66 (m, 2 H), 2.37 (m, 1 H), 2.02 (s, 3 H), 1.15 (d, J = 6.1 Hz) superimposed on m, 1.00 (s, 3 H), 0.65 (s, 3 H). Anal. Calcd for $C_{22}H_{34}ClNO_3$: C, 66.73; H, 8.64; N, 3.54. Found: C, 66.48; H, 8.57; N, 3.48.

Method B: *N*-Chloro-17β-hydroxy-4-aza-3-androstanone (5) (Typical Procedure). Lactam **4** (146 mg, 0.50 mmol) and

(23) The possibility that **28** is formed by an electrophilic chlorination of enamide **27** by the *N*-chloroazasteroid **2** was ruled out by the observation that these compounds fail to react in the dark.

(24) The 17α and 17aα configuration in **32** and **34** is based on steric arguments and is confirmed by the observation of NOE effects between the hydrogen atoms at C-17 or C-17a and the angular methyl groups C-18 of these compounds.

(25) Schwartz, N. N.; Blumbergs, J. H. *J. Org. Chem.* **1964**, *29*, 1976.

(26) Brintzinger, H.; Pfannstiel, K.; Koddebusch, H.; Kling, K. E. *Chem. Ber.* **1950**, *83*, 87.

potassium *tert*-butoxide (67 mg, 0.60 mmol) were stirred 10 min in 10 mL of THF. NCS (100 mg, 0.75 mmol) was added, and stirring was continued for 30 min. The mixture was then diluted with ether, washed three times with aqueous $NaHCO_3$ solution, dried (anhydrous $MgSO_4$), and evaporated in vacuo. The residue was separated by preparative TLC in 10% methanol–benzene to afford 146 mg (90%) of the title compound: R_f 0.45; mp 282–284 °C (from chloroform–hexane); $[\alpha]_D$ +46° (*c* 0.75); IR 3451, 1678, 1280, 1212 cm^{-1}; ^1H NMR δ 3.64 (t, *J* = 8.3 Hz, 1 H), 3.30 (dd, *J* = 12.3, 3.6 Hz, 1 H), 2.66 (m, 2 H), 1.00 (s, 3 H), 0.75 (s, 3 H). Anal. Calcd for $C_{18}H_{28}ClNO_2$: C, 66.54; H, 8.38; N, 4.31. Found: C, 66.21; H, 8.74; N, 4.31.

Similarly prepared were the following:

N-Chloro-3-methoxy-16-aza-1,3,5(10)-estratrien-17-one (12): mp 141–142 °C (from ethyl acetate–hexane); $[\alpha]_D$ +52° (*c* 2.12); IR 1720, 1497, 1254 cm^{-1}; ^1H NMR δ 7.18 (d, *J* = 8.6 Hz, 1 H), 6.76–6.63 (m, 2 H), 3.78 (s, 3 H), 3.51 (m, 2 H), 2.90 (m, 2 H), 1.07 (s, 3 H). Anal. Calcd for $C_{18}H_{22}ClNO_2$: C, 67.20; H, 6.93; N, 4.38. Found: C, 67.43; H, 6.84; N, 4.24.

N-Chloro-3-methoxy-17-aza-D-homo-1,3,5(10)-estratrien-17a-one (15): mp 145–147 °C (from ethyl acetate–hexane); $[\alpha]_D$ +90° (*c* 0.525); IR 1685, 1501, 1239, 1037 cm^{-1}; ^1H NMR δ 7.22 (d, *J* = 8.5 Hz, 1 H), 6.77–6.63 (m, 2 H), 3.79 (s, superimposed on m, total 5 H), 2.87 (m, 2 H), 1.23 (s, 3 H). Anal. Calcd for $C_{19}H_{24}ClNO_2$: C, 68.35; H, 7.25; N, 4.20. Found: C, 68.41; H, 7.45; N, 3.92.

N-Chloro-3-methoxy-17-aza-D-homo-1,3,5(10)-estratrien-16-one (22): mp 149–152 °C dec (from ethyl acetate); $[\alpha]_D$ +14° (*c* 1.435); IR 1675, 1503, 1235, 1035 cm^{-1}; ^1H NMR δ 7.20 (d, *J* = 8.5 Hz, 1 H), 6.76–6.63 (m, 2 H), 3.78 (s, 3 H), 3.57 (d, *J* = 11 Hz, 1 H), 3.38 (d, *J* = 11 Hz, 1 H), 1.09 (s, 3 H). Anal. Calcd for $C_{19}H_{24}ClNO_2$: C, 68.35; H, 7.25; N, 4.20. Found: C, 68.48; H, 7.20; N, 4.00.

Method C: N-Chloro-3-methoxy-16-aza-14β-1,3,5(10)-estratrien-15-one (18). NCS (267 mg, 2.00 mmol) in 5 mL of THF was added dropwise to a solution of lactam **17** (285 mg, 1.00 mmol) and potassium *tert*-butoxide (112 mg, 1.00 mmol) in 20 mL of THF. After 20 min of stirring, the reaction was worked up as in method B and the crude product was recrystallized from ethyl acetate–hexane to afford 234 mg (73%) of the title compound: mp 147–149 °C; $[\alpha]_D$ +184° (*c* 0.595); IR 1707, 1503, 1269, 1037 cm^{-1}; ^1H NMR δ 7.17 (d, *J* = 8.5 Hz, 1 H), 6.75–6.63 (m, 2 H), 3.78 (s, 3 H), 3.39 (d, *J* = 8.4 Hz, 1 H), 3.15 (d, *J* = 8.4 Hz, 1 H), 1.23 (s); exact mass calcd for $C_{18}H_{22}ClNO_2$ 319.1339, found 319.1341.

Isomerization of N-Chloroazasteroid 18 to 14-Chloro-3-methoxy-16-aza-1,3,5(10)-estratrien-15-one (20). *N*-Chlorolactam **18** (112 mg, 0.35 mmol) and potassium *tert*-butoxide (39 mg, 0.35 mmol) in 10 mL of THF were stirred for 45 min. The concentrated reaction mixture was separated by preparative TLC in 10% acetone–chloroform to afford 74 mg (66%) of the 14-chloro compound **20**: R_f 0.42; mp 181–183 °C (from acetone–hexane); $[\alpha]_D$ +95° (*c* 0.35); IR 3205, 3107, 1705, 1501, 1260, 1039 cm^{-1}; ^1H NMR δ 7.17 (d, *J* = 8.5 Hz, 1 H), 6.75–6.65 (m, 2 H), 6.37 (br s, 1 H), 3.79 (s, 3 H), 3.38 (d, *J* = 9.5 Hz, 1 H), 2.86 (dd superimposed on m, *J* = 9.5, 2.2 Hz, total 7 H), 1.30 (s, 3 H); ^{13}C NMR δ 174.9 (C-15), 78.8 (C-14); mass spectrum, *m/e* (relative intensity) 321 (M^+, ^{37}Cl, 7), 319 (M^+, ^{35}Cl, 20), 283 (M^+ – HCl, 72), 268 (36), 174 (58), 43 (100). Anal. Calcd for $C_{18}H_{22}ClNO_2$: C, 67.60; H, 6.93; N, 4.38. Found: C, 67.88; H, 7.00; N, 4.13.

Reactions of N-Chloroazasteroids with Thiols. Reaction of N-Chloroazasteroid 2 with Benzenethiol (Typical Procedure). Benzenethiol (29 μL, 0.28 mmol) was added over 15 min to the *N*-chloro compound **2** (118 mg, 0.28 mmol) in 3 mL of chloroform. A yellow-orange color rapidly developed. After 10 min, triethylamine (39 μL, 0.28 mmol) was added slowly, and the orange color was discharged toward the end of the addition. The colorless solution was concentrated and separated by preparative TLC in 25% ethyl acetate–hexane to afford: (A) Diphenyl disulfide (20 mg, 66%), identical with an authentic sample. (B) *N*-(Phenylthio)-4-aza-3-cholestanone (**3**) (43 mg, 31%) as a gum: R_f 0.31; IR 1682, 1273, 1216 cm^{-1}; ^1H NMR δ 7.4–7.1 (complex, 5 H), 3.34 (m, 1 H), 2.70 (m, 2 H), 0.99 (s, 3 H), 0.89 and 0.86 (2 overlapping d, 9 H total), 0.65 (s, 3 H); mass spectrum, *m/e* (relative intensity) 495 (M^+, 5), 206 (21), 109 (PhS^+, 60), 83 (100); exact mass calcd for $C_{32}H_{49}NOS$ 495,3535, found 495,3537. (C) Lactam **1** (72 mg, 66%), identical with an authentic sample.

The reactions of *N*-chloroazasteroids **7**, **12**, and **15** with benzenethiol were performed similarly, except that THF was employed as the solvent in the case of **12** and **15**. The properties of the resulting *N*-thiolactams were as follows:

17β-Acetoxy-N-(phenylthio)-4-aza-3-androstanone (8): yield 33%; IR 1732, 1674, 1250, 1034 cm^{-1}; ^1H NMR δ 7.4–7.15 (complex, 5 H), 4.59 (t, *J* = 8.3 Hz, 1 H), 3.35 (dd, *J* = 12.0, 3.8 Hz, 1 H), 2.71 (m, 2 H), 2.04 (s, 3 H), 0.92 (s, 3 H), 0.78 (s, 3 H); mass spectrum, *m/e* (relative intensity) 441 (M^+, 4), 154 (32), 43 (100); exact mass calcd for $C_{26}H_{35}NO_3S$ 441.2338, found 441.2334.

3-Methoxy-N-(phenylthio)-16-aza-1,3,5(10)-estratrien-17-one (13): yield 16%; mp 142–144 °C (from chloroform–hexane); IR 1720, 1502, 1235, 1094 cm^{-1}; ^1H NMR δ 7.34–7.17 (complex, d at δ 7.20, *J* = 8.9 Hz, total 6 H), 6.76–6.63 (m, 2 H), 3.78 (s, 3 H), 3.52–3.46 (m, 2 H), 2.90–2.84 (m, 2 H), 1.04 (s, 3 H); mass spectrum, *m/e* (relative intensity) 393 (M^+, 51), 228 (39), 160 (69), 109 (100); exact mass calcd for $C_{24}H_{27}NO_2S$ 393.1762, found 393.1764.

3-Methoxy-N-(phenylthio)-17-aza-D-homo-1,3,5(10)-estratrien-17a-one (16): yield 32%; IR 1669, 1501, 1239, 1158 cm^{-1}; ^1H NMR δ 7.38–7.21 (complex, 6 H), 6.77–6.65 (m, 2 H), 3.84–3.68 (complex, s at 3.78, total 5 H), 2.88 (m, 2 H), 1.24 (s, 3 H); mass spectrum, *m/e* (relative intensity) 407 (M^+, 88), 173 (68), 147 (78), 109 (100); exact mass calcd for $C_{25}H_{29}NO_2S$ 407.1919, found 407.1904.

Reaction of N-Chloroazasteroid 18 with L-Cysteine Ethyl Ester Hydrochloride. A mixture of triethylamine (28 μL, 0.20 mmol) and L-cysteine ethyl ester hydrochloride (37 mg, 0.20 mmol) in 10 mL of THF was added dropwise to the *N*-chloro compound **18** (64 mg, 0.20 mmol) in THF. After 30 min, the mixture was concentrated in vacuo, taken up in ethyl acetate, and washed with water and aqueous NaCl solution. The organic layer was dried (anhydrous $MgSO_4$), concentrated, and separated by preparative TLC in 20% acetone–chloroform to afford: (A) Lactam **17** (43 mg, 76%), identical with an authentic sample. (B) The cysteinyl *N*-thiolactam **23** (7.3 mg, 8%): R_f 0.19; IR 3366, 3291, 1736, 1703, 1609, 1501, 1262, 1234, 1190, 1038 cm^{-1}; ^1H NMR δ 7.17 (d, *J* = 8.7 Hz, 1 H), 6.74–6.62 (m, 2 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 3.79 (s, 3 H), 3.67 (m, 1 H), 3.40 (d, *J* = 9.3 Hz, 1 H), 3.10 (d, *J* = 9.3 Hz, superimposed on m, total 2 H), 1.30 (t, *J* = 7.4 Hz, 3 H), 1.19 (s, 3 H); mass spectrum, *m/e* (relative intensity) 432 (M^+, 0.9), 187 (33), 98 (100).

Reaction of N-Chloroazasteroid 5 with Benzenethiol. Benzenethiol (39 μL, 0.38 mmol) was added over 10 min to *N*-chloroazasteroid **5** (125 mg, 0.38 mmol) in 2 mL of chloroform. Triethylamine (53 μL, 0.38 mmol) was then added over 10 min to the turbid, orange solution, which turned colorless and clear toward the end of the addition. The mixture was concentrated and separated by preparative TLC in 10% methanol–benzene to afford: (A) Diphenyl disulfide (31 mg, 74%), identical with an authentic sample. (B) A mixture of sulfenate ester **24a** and the two diastereomers of sulfinate ester **24b** (total 35 mg, 23%), with ^1H NMR signals (t) at δ 3.69, 4.08 and 4.17. Repeated recrystallization from methanol afforded a pure diastereomer of **24b**: mp 254–255 °C; IR ($CHCl_3$) 3397, 1656, 1126 cm^{-1}; ^1H NMR δ 7.8–7.7 (m, 2 H), 7.6 (m, 3 H), 5.86 (s, exchanged with D_2O, 1 H), 4.08 (t, *J* = 8.5 Hz, 1 H), 3.02 (m, 1 H), 2.40 (m, 2 H), 0.88 (s, 3 H), 0.79 (s, 3 H). Anal. Calcd for $C_{24}H_{33}NO_3S$: C, 69.35; H, 8.00; N, 3.37. Found: C, 69.20; H, 8.30; N, 3.50. (C) Lactam **4** (86 mg, 77%), identical with an authentic sample.

Reaction of Lactam 4 with Benzenesulfenyl Chloride. Benzenesulfenyl chloride (0.15 mL of a 1.0 M solution in chloroform, 0.15 mmol) was added to lactam **5** (29 mg, 0.10 mmol) in 2 mL of THF. After 3 min, triethylamine (21 μL, 0.15 mmol) was added dropwise over ca. 2 min, and the solution was allowed to stir for an additional 15 min. Preparative TLC in 10% methanol–benzene[27] afforded 17 mg (43%) of sulfenate ester **24a**: R_f 0.41; mp 200–201 °C (from chloroform–hexane); IR ($CHCl_3$) 3396, 1656 cm^{-1}; ^1H NMR δ 7.4–7.1 (complex, 5 H), 5.41 (br s,

(27) In several instances we observed that the sulfenate ester **24a** underwent partial decomposition upon preparative TLC on silica gel to form the lactam **4** and other products. This may be suppressed by developing the plates only ca. 8–10 cm to minimize contact time, and by not activating them by heating prior to use.

1 H), 3.69 (t, J = 8.4 Hz, 1 H), 3.04 (m, 1 H), 2.41 (m, 2 H), 0.91 (s, 3 H), 0.84 (s, 3 H); mass spectrum, m/e (relative intensity) 399 (M^+, 4), 274 (M^+ - PhSO, 100); exact mass calcd for $C_{24}H_{33}NO_2S$ 399.2232, found 399.2225.

When the reaction was repeated in chloroform solution with 0.3 mmol of the sulfenyl chloride and a delay of 30 min prior to the addition of 0.3 mmol of triethylamine, the principal product was **24b** (NMR analysis).[28]

Oxidation of Sulfenate Ester 24a with MCPBA. The sulfenate ester **24a** (35 mg, 0.088 mmol) and MCPBA (15 mg, 0.087 mmol) were stirred in 5 mL of chloroform for 15 min. The solution was then washed three times with aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, and evaporated in vacuo. NMR analysis of the residue revealed the presence of both diastereomers of sulfinate ester **24b**, as well as a small amount of sulfonate ester **25**. The product was further treated with 18 mg (0.105 mmol) of MCPBA and worked up as before, resulting in the complete conversion of **24b** to **25**. When the product mixture from the reaction of N-chloroazasteroid **5** with benzenethiol was similarly oxidized with excess MCPBA, **25** was again produced, mp 226–227 °C (from chloroform–hexane). This was identical with a sample of **25** prepared from the reaction of **4** with benzenesulfonyl chloride in pyridine containing a catalytic amount of 4-(N,N-dimethylamino)pyridine (DMAP): mp 228–230 °C (from methanol); IR ($CHCl_3$) 3395, 1655, 1360, 1186, 1176 cm^{-1}; ^1H NMR δ 7.92 (m, 2 H), 7.7–7.5 (m, 3 H), 5.65 (s, 1 H), 4.29 (t, J = 7.2 Hz, 1 H), 3.02 (m, 1 H), 2.39 (m, 2 H), 0.88 (s, 3 H), 0.81 (s, 3 H). Anal. Calcd for $C_{24}H_{33}NO_4S$: C, 66.79; H, 7.71; N, 3.25. Found: C, 66.98; H, 7.77; N, 2.99.

Photolyses of N-Chloroazasteroids. N-Chloro-4-aza-3-cholestanone (2). The title compound (31.5 mg, 0.075 mmol) in 5 mL of methanol was irradiated for 15 min. The solvent was then evaporated, and the residue was separated by preparative TLC in 50% ethyl acetate–hexane to afford: (A) 7.6 mg (24%) of 6-chloro-4-aza-5-cholesten-3-one (**28**): R_f 0.57; IR 3241, 1691, 1225 cm^{-1}; ^1H NMR δ 7.53 (br s, 1 H), 2.52 (m, 2 H), 2.36 (m, 1 H), 1.13 (s, superimposed on m), 0.92 (d, J = 6.5 Hz, 3 H), 0.87 (2 closely overlapping d each with J = 6.5 Hz, total 6 H), 0.71 (s, 3 H); ^{13}C NMR δ 168.9, 134.9, 108.2; mass spectrum, m/e (relative intensity) 419 (M^+, 100) 384 (9), 264 (13); exact mass calcd for $C_{26}H_{42}ClNO$ 419.2955, found 419.2958. (B) 4.0 mg (14%) of 4-aza-5-cholesten-3-one (**27**): R_f 0.23, identical with an authentic sample[29] (TLC, IR, NMR). (C) 15.4 mg (53%) of 4-aza-3-cholestanone (**1**), identical with an authentic sample (TLC, IR, NMR).

N-Chloro-3-methoxy-17-aza-D-homo-1,3,5(10)-estratrien-17a-one (15). The title compound (85 mg, 0.255 mmol) in 10 mL of methanol was irradiated for 2 h. The solvent was evaporated, and the residue was separated by preparative TLC in 30% acetone–chloroform to afford 14.7 mg (22%) of 3-methoxy-17-aza-D-homo-1,3,5(10),15-estratetraen-17a-one (**30**): R_f 0.67; IR ($CHCl_3$) 3421, 1678, 1648, 1501 cm^{-1}; ^1H NMR δ 7.24 (d, J = 9.8 Hz, 1 H), 7.16 (br s, 1 H), 6.77–6.65 (m, 2 H), 6.15 (m, 1 H), 5.25 (crude d, J = 7.5 Hz, 1 H), 3.79 (s, 3 H), 2.90 (m, 2 H), 1.05 (s, 3 H); mass spectrum, m/e (relative intensity) 297 (M^+, 85), 282 (34), 186 (39), 84 (92), 55 (100); exact mass calcd for $C_{19}H_{23}NO_2$ 297.1729, found 297.1728.

N-Chloro-3-methoxy-16-aza-14β-1,3,5(10)-estratrien-15-one (18). The title compound (80 mg, 0.25 mmol) in 10 of methanol was irradiated for 1.5 h. The solvent was evaporated, and the residue was separated by preparative TLC in 30% benzene–ethyl acetate to afford: (A) 16.7 mg (21%) of 3,17α-dimethoxy-16-aza-14β-1,3,5(10)-estratrien-15-one (**32**): R_f 0.59; IR 3241, 1706, 1502, 1263, 1093, 1038 cm^{-1}; ^1H NMR δ 7.17 (d, J = 8.6 Hz, 1 H), 6.95 (br s, 1 H), 6.74–6.62 (m, 2 H), 4.10 (d, J = 1.5 Hz, 1 H), 3.78 (s, 3 H), 3.33 (s, 3 H), 2.84 (m, 2 H), 1.19 (s, 3 H); mass spectrum, m/e (relative intensity) 315 (M^+, 18), 283 (M^+ - MeOH, 23), 186 (63), 128 (35), 31 (100); exact mass calcd for $C_{19}H_{25}NO_3$ 315.1834, found 315.1836. (B) 34.8 mg (49%) of 3-methoxy-16-aza-14β-1,3,5(10)-estratrien-15-one (**17**), identical with an authentic sample (TLC, IR, NMR).

N-Chloro-3-methoxy-17-aza-D-homo-1,3,5(10)-estratrien-16-one (22). The title compound (83.9 mg, 0.25 mmol) in 10 mL of methanol was irradiated for 1.5 h. The solvent was evaporated, and the residue was separated by preparative TLC in 30% benzene–acetone to afford: (A) Crude 3,17aα-dimethoxy-17-aza-D-homo-1,3,5(10)-estratrien-16-one (**34**); 30.0 mg, R_f 0.48. This was further purified by preparative HPLC to afford 19.7 mg (24%) of homogeneous **34**: IR 3206, 1664, 1086 cm^{-1}; ^1H NMR δ 7.41 (br d, J = 4.0 Hz, 1 H), 7.22 (d, J = 8.7 Hz, 1 H), 6.76–6.63 (m, 2 H), 3.92 (d, J = 4.3 Hz, 1 H), 3.79 (s, 3 H), 3.40 (s, 3 H), 0.99 (s, 3 H); mass spectrum, m/e (relative intensity) 329 (M^+, 59), 297 (M^+ - MeOH, 100) 228 (88), 186 (58), 101 (85); exact mass calcd for $C_{20}H_{27}NO_3$ 329.1991, found 329.1986. (B) 3-Methoxy-17-aza-D-homo-1,3,5(10)-estratrien-16-one (**21**), 33.4 mg (45%), identical with an authentic sample (TLC, IR, NMR).

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(28) In several experiments where **4** was treated with a large excess of the sulfenyl chloride in chloroform solution, we observed the substantial formation of an N-sulfenylated product that was only partly characterized. Its ^1H NMR spectrum showed no NH signal and revealed substantial shifts to lower field of the signals associated with the protons at C-5 (δ 3.34) and C-2 (δ 2.72) relative to the corresponding ones in azasteroid **4** (δ 3.05 and 2.42, respectively).

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