in 4.5 ml of 1.00 *N* NaOH and the resulting mixture was refluxed for 9 hr. The cooled reaction mixture was extracted with two 5-ml portions of chloroform, and the aqueous layer was saturated with sodium chloride and then extracted with two 5-ml portions of chloroform. The chloroform were evaporated and the residue was sublimed at 0.25 mm to yield 97.5% of a mixture of oxides (**3**), mp 73–133°.

Anal. Calcd for $C_{12}H_{17}OP$: C, 69.21; H, 8.23. Found: C, 69.47; H, 8.20.

This mixture was analyzed by TLC as described above for the cleavage products of 4-methyl-1,1-diphenylphosphorinanium bromide (**11**) and gave 78% **3b** and 22% **3a**.

The cis isomer of **10** was similarly cleaved to give a hygroscopic mixture of oxides.

Anal. Calcd for $C_{12}H_{17}OP \cdot \frac{1}{4}H_2O$: C, 67.74; H, 8.29. Found: C, 67.93; H, 8.39.

The analysis of this mixture gave 52% **3b** and 48% **3a**.

Acknowledgments. The assistance of R. H. Bowman and F. B. Burns with exploratory work on the synthesis of alkoxyphosphonium salts is gratefully recognized. Appreciation is expressed to Dr. C. G. Willson for 220-MHz spectra determinations. The author is also indebted to the National Science Foundation for support under Grants GP-7407 and GP-25479.

Registry No.—*cis*-**1**, 55043-89-5; *trans*-**1**, 55043-91-9; *cis*-**2**, 55043-93-1; *trans*-**2**, 55043-95-3; **3a**, 55043-96-4; **3b**, 55043-97-5; **4a**, 55043-98-6; **4b**, 55043-99-7; *cis*-**5**, 54932-29-5; *trans*-**5**, 55044-00-3; *cis*-**10**, 55044-01-4; *trans*-**10**, 55044-02-5; **11**, 55044-03-6; trimethyloxonium hexafluorophosphate, 12116-05-1.

References and Notes

(1) (a) K. L. Marsi, *Chem. Commun.*, 846 (1968); (b) *J. Am. Chem. Soc.*, **91**, 4724 (1969); (c) W. Egan, G. Chauviere, K. Mislow, R. T. Clark, and K. L. Marsi, *Chem. Commun.*, 733 (1970); (d) K. L. Marsi and R. T. Clark, *J. Am. Chem. Soc.*, **92**, 3791 (1970); (e) K. L. Marsi, *ibid.*, **93**, 6341 (1971); (f) K. L. Marsi, F. B. Burns, and R. T. Clark, *J. Org. Chem.*, **37**, 238 (1972); K. L. Marsi and J. E. Oberlander, *J. Am. Chem. Soc.*, **95**, 200 (1973).
(2) G. Zon, K. E. DeBruin, K. Naumann, and K. Mislow, *J. Am. Chem. Soc.*, **91**, 7023 (1969).
(3) A. Fitzgerald, C. N. Caughlin, and K. L. Marsi, manuscript submitted.
(4) J. A. Hirsch, *Top. Stereochem.*, **1**, 199 (1967).
(5) E. W. Garbisch, Jr., and D. B. Patterson, *J. Am. Chem. Soc.*, **85**, 3228 (1963).
(6) J. I. Musher, *Spectrochim. Acta.*, **16**, 835 (1960).
(7) F. A. L. Anet, *Can. J. Chem.*, **39**, 2262 (1961).
(8) In a previous communication (ref 1d) the coupling constants for **3a** and **3b** were erroneously interchanged. The chemical shifts and coupling constants for methyl protons for the cis and trans isomers of the analogous 4-methyl-1-phenylcyclohexanol compare well with those for **3a** and **3b**. They are as follows: trans alcohol, δ 0.92 (J = 6 Hz); cis alcohol, δ 0.99 (J = 0 Hz) [J. R. Luderer, J. E. Woodall, and J. L. Pyle, *J. Org. Chem.*, **36**, 2909 (1971)].
(9) H. E. Shook, Jr., and L. D. Quin, *J. Am. Chem. Soc.*, **89**, 1841 (1967); J. I. Musher, *ibid.*, **83**, 1146 (1961).
(10) G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, 4284 (1954); E. L. Eliel and R. G. Haber, *J. Org. Chem.*, **23**, 2041 (1958); N. L. Allinger and R. J. Curby, Jr., *ibid.*, **26**, 933 (1961); E. R. Ward, W. H. Poesche, D. Higgins, and D. D. Heard, *J. Chem. Soc.*, 2374 (1962); J. A. Zderic, M. E. C. Rivera, and D. C. Limon, *J. Am. Chem. Soc.*, **82**, 6373 (1960); S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955); H. E. Zimmerman, *ibid.*, **79**, 6554 (1957).
(11) M. J. Gallagher and I. D. Jenkins, *Top. Stereochem.*, **3**, 6 (1968).
(12) Oxides **4a**, **4b**, **3a**, and **3b** have been determined to be stereochemically stable under these reaction conditions (ref 1c,d,f); cf. also R. B. Wetzel and G. L. Kenyon, *J. Am. Chem. Soc.*, **96**, 5199 (1974).
(13) L. Horner, *Pure Appl. Chem.*, **9**, 225 (1964); L. D. Quin and T. P. Barket, *J. Am. Chem. Soc.*, **92**, 4303 (1970).
(14) D. G. Gorenstein, *J. Am. Chem. Soc.*, **94**, 2808 (1972).
(15) K. Mislow, *Acc. Chem. Res.*, **3**, 321 (1970).
(16) W. E. McEwen, K. F. Kumli, A. Blade-Font, M. Zanger, and C. A. VanderWerf, *J. Am. Chem. Soc.*, **86**, 2378 (1964).
(17) Y. Kashman and O. Awerbach, *Tetrahedron*, **26**, 4213 (1970).
(18) K. E. DeBruin, G. Zon, K. Naumann, and K. Mislow, *J. Am. Chem. Soc.*, **91**, 7027 (1969).
(19) K. L. Marsi and J. E. Oberlander, *J. Am. Chem. Soc.*, **95**, 200 (1973). The principal product results from ring opening.
(20) (a) S. E. Cremer, B. C. Trevidi, and F. L. Weitl, *J. Org. Chem*, **36**, 3226 (1971); (b) A. Streitwieser, Jr., "Solvolytic Displacement Reactions", McGraw-Hill, New York, N.Y., 1962, p 73.
(21) K. E. DeBruin and S. Chandrasekaran, *J. Am. Chem. Soc.*, **95**, 974 (1973).
(22) Melting points of alkoxyphosphonium salts and phosphine oxides were determined in sealed tubes. Phosphines were handled in a dry nitrogen atmosphere. ^{18}O analyses were performed by West Coast Technical Service, Inc., Cerritos, Calif.
(23) K. L. Marsi, D. M. Lynch, and G. D. Homer, *J. Heterocycl. Chem.*, **9**, 331 (1972).
(24) K. Marsi, *J. Org. Chem*, **39**, 265 (1974).

Concerning the Mechanism of the Characteristic Ring D Fragmentation of Steroids[1]

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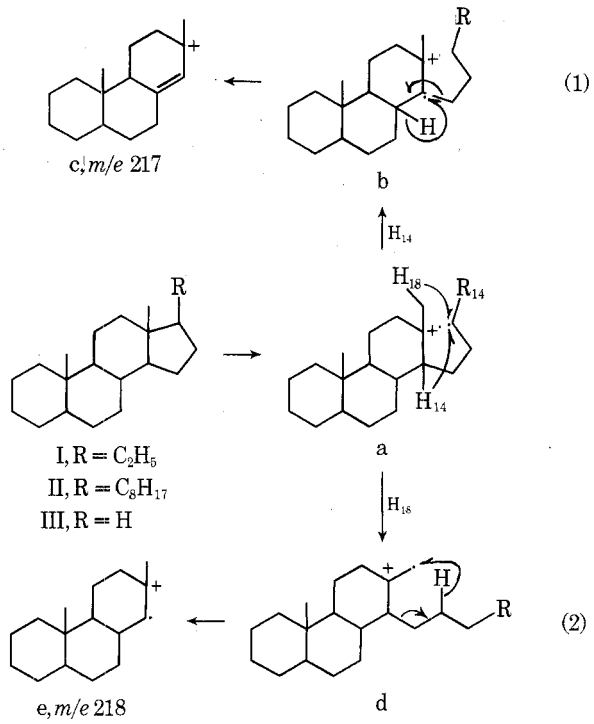
The electron impact induced fragmentations of $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene (VI) and $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene (VII) were investigated. Both compounds and appropriate deuterium-labeled analogs fragmented in accord with the existing mechanistic proposal for the characteristic ring D fragmentation of steroids. First field-free region metastable intensities were consistent with structural identity among the *m/e* 217 ions from 5α-pregnane and the *D*-seco steroids, and among the *m/e* 218 ions from the same sources; widely divergent metastable intensities were observed from known isomeric ions. Evidence was obtained for significant interconversion of the molecular ions of VI and VII. The results of these experiments lend powerful support to the previously proposed ring D fragmentation mechanisms.

The most conspicuous peaks in the mass spectra of steroid hydrocarbons such as pregnane (I) or cholestane (II) appear at *m/e* 217 and 218, corresponding to the elimination of ring D and the side chain at C-17.[2] Since these fragmentations persist even in highly functionalized steroids, and since they are of obvious diagnostic importance (they define the molecular weight of the side chain at C-17), a number of investigators have attempted to determine the mechanisms by which these peaks arise. Initially, this was an area of some controversy.[3-5] The elegant and extensive deuterium-labeling experiments of Djerassi[2] provided data which permitted formulation of a plausible mechanism for the genesis of these ubiquitous peaks (Scheme I).

Initial charge localization in the C-13–C-17 bond (I → a) was postulated, since it results in the formation of a stable tertiary carbonium ion and a secondary (R = alkyl) or primary (R = H) radical site, and relieves the strain inherent in the trans hydrindan ring system. Deuterium-labeling experiments demonstrated that the genesis of the *m/e* 217 ion (c) involved transfer of the C-14 hydrogen atom to the eliminated moiety; such a process appears plausible, since it generates an ionized double bond between C-13 and

Scheme I



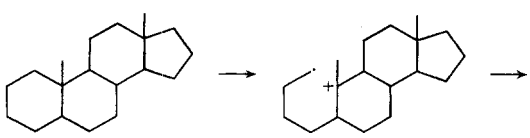
(1)

(2)

C-14, more stable than the ionized single bond at C-13–C-17. Cleavage of the C-14–C-15 bond of ion b generates *m/e* 217 (eq 1).

The formation of the *m/e* 218 ion was shown to be even more remarkable; a reciprocal hydrogen transfer from C-18 to the eliminated moiety and from C-16 to the charge retaining species was demonstrated. The mechanism depicted in eq 2 was therefore postulated; hydrogen transfer from C-18 to the C-17 radical site (a → d) appeared favorable, since it again generates an ionized double bond. Back transfer of a hydrogen atom from C-16 and cleavage of the C-14–C-15 bond generates the *m/e* 218 ion (d → e). Deuterium-labeling experiments on androstane (III),[6] *D*-homo steroids,[7] and 14α-methyl steroids[8] have been in complete accord with the above formulation. Nevertheless, several aspects of this unusual fragmentation mechanism merit further investigation.

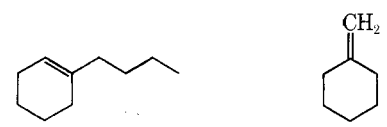
First, charge localization in the C-13–C-17 bond is an essential step in the mechanisms depicted in Scheme I. For pregnane, this appears plausible; cleavage generates a tertiary carbonium ion and a secondary radical site,[2] and relieves two skew butane interactions (C_{20}–C_{17}–C_{13}–C_{18} and C_{20}–C_{17}–C_{13}–C_{12}) and the strain inherent in a trans-fused hydrindan.[7] For many other steroids, however, the apparent site of preferred charge localization does not correspond to the most frangible bond. In androstane, for example, the predominant mode of fragmentation involves cleavage of ring A. Deuterium-labeling experiments have domonstrated that the mechanisms are directly analogous to that depicted in Scheme I;[6] initial charge localization is postulated in the C-1–C-10 bond (eq 3). Such charge localization generates a tertiary carbonium ion and a primary radical site, and relieves a single gauche butane interaction (C_1–C_{10}–C_9–C_{11}). A priori, charge localization in the C-9–C-10 bond, for example, appears more favorable; a tertiary carbonium ion and a secondary radical site are generated, and three skew butane interactions are relieved (C_1–C_{10}–C_9–C_{11}, C_1–C_{10}–C_9–C_8, C_{19}–C_{10}–C_9–C_8). It is suprising that little fragmentation appears to occur from this charge-localized species, particularly in light of the demonstrated sensitivity of charge localization of steric effects.[7]



(3)

Another aspect of the formulation of Scheme I which appears troubling is the failure of the C_{12} hydrogens to participate in these reactions. Abstraction of a C-14 hydrogen, rationalized because it generates an ionized double bond, results in the formation of *m/e* 217. Abstraction of the C-18 hydrogen, again considered propitious because it forms an ionized double bond, produces *m/e* 218. However, abstraction of a C-12 hydrogen atom also generates an ionized double bond; furthermore, the ring size involved in such a hydrogen migration is identical with that required for migration of a C-18 hydrogen. The migratory aptitude of the secondary C-12 hydrogen atoms should be larger than that of the primary C-18 hydrogens, since secondary hydrogens are more mobile than primary ones.[9] Nevertheless, deuterium-labeling experiments demonstrate that abstraction of a C-12 hydrogen is not a major pathway in the characteristic ring D cleavage.

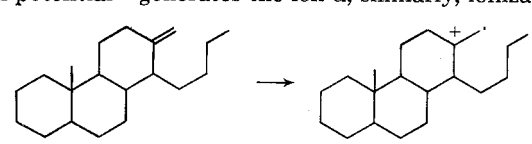
Finally, it is interesting to note that intermediate ions b and d correspond formally to ionized alkenes. Deuterium-labeling experiments[2] show clearly that these ions do not interconvert significantly before fragmentation. This observation is unexpected in light of the reports indicating that extensive double bond isomerization precedes fragmentation in structurally related alkenes such as IV and V.[10]



IV V

Because of these troubling inconsistencies and the preeminent position of this much-studied mechanism among steroid fragmentations, further investigation appeared warranted. Further, metastable data indicate that these ions are themselves precursors of many abundant low-mass ions in steroid mass spectra.[2,11] If significant structural information is to be gleaned from these low-mass ions, the structures of the precursor ions must be firmly elucidated. Thus, an investigation of the electron impact induced behavior of $\Delta^{13(18)}$-13,17-seco-*D*-homoandrostene (VI) and $\Delta^{13(14)}$-13,17-seco-*D*-homoandrostene (VII) was launched.

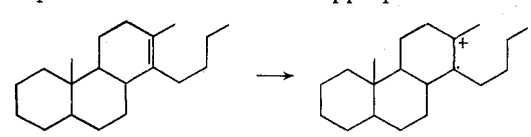
Ionization of the exocyclic alkene VI with subsequent charge localization in the functional group of lowest ionization potential[12] generates the ion d; similarly, ionization of



(4)

VI d

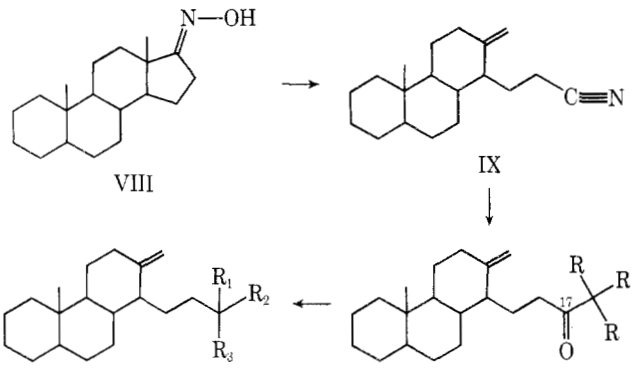
the endocyclic isomer VII generates ion b. Analysis of the mass spectra of VI and VII and appropriate deuterium-labeled analogs should establish whether these ions fragment in accord with Scheme I, and whether fragmentation pre-



(5)

VII b

Scheme II



VIII IX X, R = H

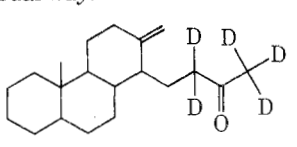
XI, R_1 = H; R_2 = OH; R_3 = CH_3
XII, R_1 = H; R_2 = OTs; R_3 = CH_3
VI, R_1 = R_2 = H; R_3 = CH_3
XIV, R_1 = R_2 = H; R_3 = CD_3
XV, R_1 = D; R_2 = OH; R_3 = CH_3
XVI, R_1 = D; R_2 = OTs; R_3 = CH_3
XVII, R_1 = R_2 = D; R_3 = CH_3

XIII, R = D

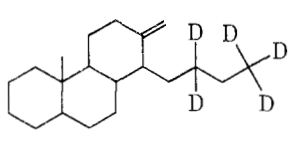
cedes isomerization. If these molecules do, indeed, generate *m/e* 217 and 218, metastable defocusing experiments can be utilized to ascertain whether these ions are structurally identical with those produced from authentic steroids, such as pregnane (I). In addition, since the electron impact induced behavior of alkenes remains a subject of continuing investigations,[10,13] the fragmentations of these compounds should be of intrinsic interest.

Synthesis of Labeled and Unlabeled *D*-Seco Alkenes. The synthesis of the exocyclic alkene $\Delta^{13(18)}$-13,17-seco-*D*-homoandrostene (VI) is depicted in Scheme II. Beckmann rearrangement of 5α-androstan-17-one oxime (VIII),[14] according to the procedure of Barton,[15] gave an 11% yield of the "abnormal" Beckmann product $\Delta^{13(18)}$-13,17-seco-5α-androstene-17-nitrile (IX). Treatment of the nitrile with methyllithium gave the ketone $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-one (X). Lithium aluminum hydride reduction gave the corresponding alcohol, $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-ol (XI); conversion to the tosylate XII and further lithium aluminum hydride reduction gave the desired hydrocarbon, $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene (VI).

For the purposes of this study it became necessary to prepare derivatives deuterium labeled at C-17a, C-17, and C-16. Reaction of the nitrile IX with trideuteriomethyllithium gave the ketone $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-one-*17a,17a,17a-d*$_3$ (XIII). Conversion to the hydrocarbon in the usual way gave $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene-*17a,17a,17a-d*$_3$ (XIV) in 63% isotopic purity. Reduction of the ketone X with lithium aluminum deuteride gave $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-ol-*17-d*$_1$ (XV); conversion to the tosylate XVI and reduction with lithium aluminum deuteride gave the desired hydrocarbon $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene-*17,17-d*$_2$ (XVII, 96% d_2). Repeated base-catalyzed exchanges (D_2O–CH_3OD–K_2CO_3) of the ketone X gave the pentadeuterated ketone XVIII; conversion to the hydrocarbon XIX ($\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene-*16,16,17a,17a,17a-d*$_5$, 89% d_5) was accomplished in the usual way.

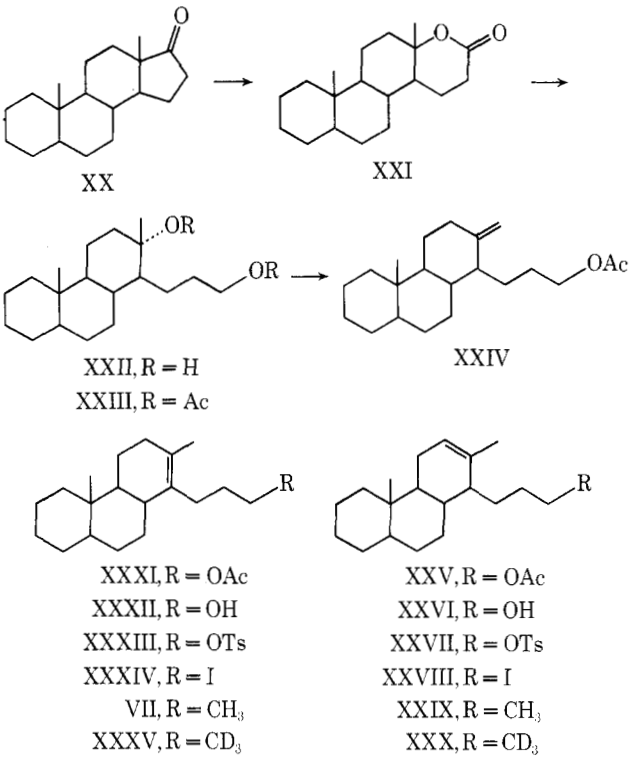


XVIII



XIX

Scheme III



XX XXI

XXII, R = H
XXIII, R = Ac

XXIV

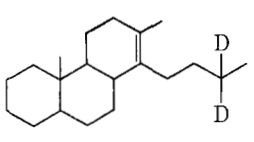
XXXI, R = OAc
XXXII, R = OH
XXXIII, R = OTs
XXXIV, R = I
VII, R = CH_3
XXXV, R = CD_3

XXV, R = OAc
XXVI, R = OH
XXVII, R = OTs
XXVIII, R = I
XXIX, R = CH_3
XXX, R = CD_3

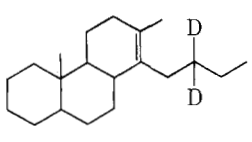
The synthesis of $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene (VII) is depicted in Scheme III. Baeyer–Villiger oxidation of 5α-androstan-17-one (XX)[16] with peroxytrifluoroacetic acid yielded 5α-androstane-13,17-seco-17-oic acid lactone (XXI);[17] lithium aluminum hydride reduction gave 13,17-seco-5α-androstan-13α,17-diol (XXII).

Pyrolysis of the diacetate XXIII gave a mixture of three alkene acetates in which the desired isomer ($\Delta^{13(14)}$-13,17-seco-5α-androstene 17-acetate, XXXI) was predominant. Thin layer chromatography on silica gel impregnated with 10% silver nitrate[18] removed the exocyclic isomer XXIV; removal of the endocyclic impurity XXV was postponed until the acetates had been converted to the hydrocarbons. Hydrolysis of the isomeric mixture of alkenes to the corresponding alcohols (XXVI and XXXII), formation of the tosylates (XXVII and XXXIII), and then treatment with sodium iodide in acetone gave the isomeric mixture of the iodides (XXVIII and XXXIV). Homologation with lithium dimethylcopper followed by thin layer chromatography on silica gel–silver nitrate gave isomerically pure $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene (VII).

Preparation of $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene-*17a,17a,17a-d*$_3$ (XXXV) was accomplished by reaction of the isomeric iodide mixture with lithium perdeuteriodimethylcopper. After silica gel–silver nitrate chromatography, the desired alkene was obtained in 95% isotopic purity. Reduction of the lactone XXI with lithium aluminum deuteride gave 13,17-seco-5α-androstane-13α,17-diol-*17,17-d*$_2$. The diol was converted to $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene-*17,17-d*$_2$ (XXXVI, 97% d_2) in the usual manner. Finally, reaction of 5α-androstane-17-one-*16,16-d*$_2$[14] according to the usual procedure gave $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene-*16,16-d*$_2$ (XXXVII) in 97% isotopic purity.



XXXVI



XXXVII

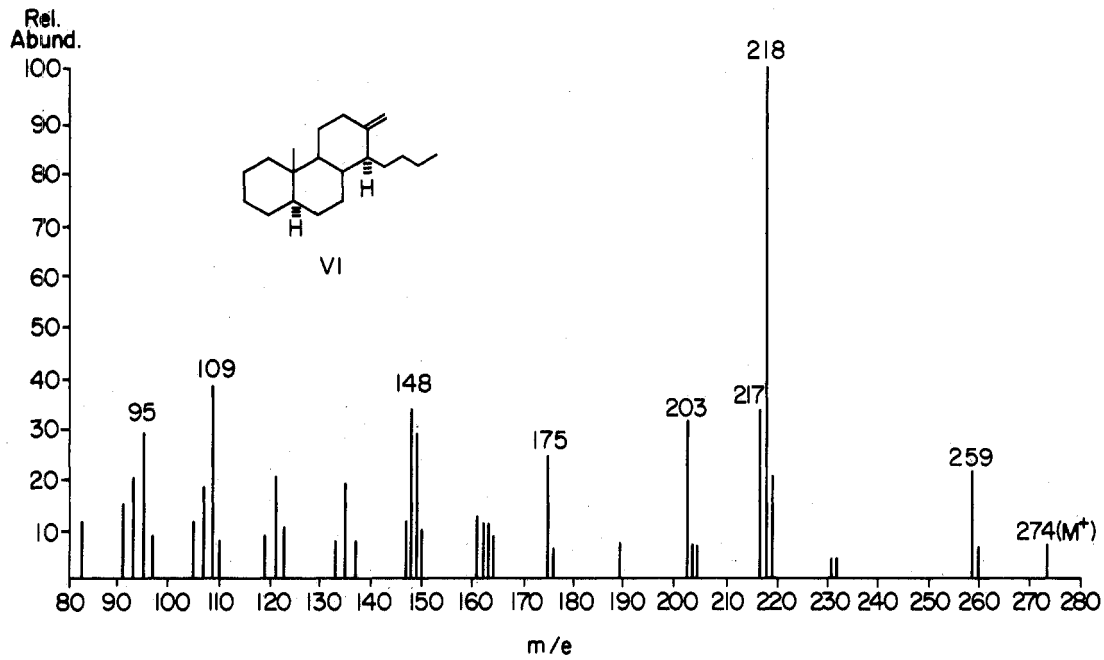


Figure 1.

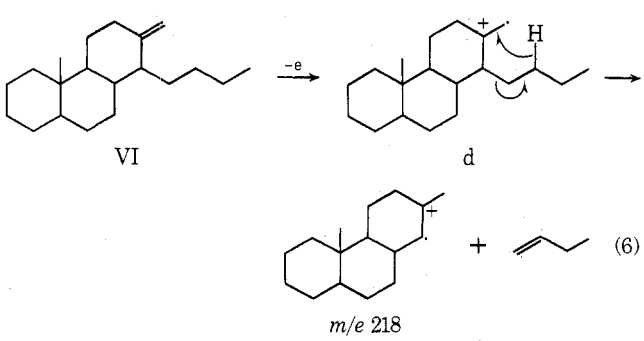
Table I
Shifts[a] of Peaks Corresponding to Ring D in $\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrostene (VI)

Compd	Isotopic purity, %	M^+	$M - C_3H_6$	$M - C_4H_8$	$M - C_4H_9$
$-d_0$		274	232	218	217
$-17a,17a,17a-d_3$	d_3 63	277	232	218	217
$-17,17-d_2$	d_2 96	276	233	218 (80%)	217 (90%)
				219 (20%)	218 (10%)
$-16,16,17a,17a,17a-d_5$	d_5 89	279	232	219	217 (75%)
					218 (25%)

[a] Reported shifts are corrected for isotopic impurity as well as ^{13}C contributions and are greater than 95% unless otherwise indicated.

Results and Discussion

Ionization of $\Delta^{13(18)}$-13,17-seco-*D*-homoandrostene (VI) and subsequent charge localization in the carbon–carbon double bond generates ion d. The mechanism depicted in Scheme I predicts that d fragments to give an ion of *m/e* 218. Inspection of Figure 1 indicates that such behavior indeed occurs; *m/e* 218 is the base peak in the spectrum of the alkene VI. Deuterium-labeling experiments were performed in order to ascertain the mechanism of formation of *m/e* 218. The results obtained (Table I) were in full accord with the formulation of Scheme I. Labels at C-17a and C-17 were largely eliminated, while a deuterium from C-16 was transferred to the charge-retaining moiety (eq 6).



(6)

These observations clearly establish that d fragments to generate *m/e* 218; they do not, however, exclude the possibility that the *m/e* 218 ion in steroid mass spectra arises by a different mechanism and generates an isomeric *m/e* 218 ion. Metastable defocusing experiments[19,20] were therefore performed to determine whether the *m/e* 218 ion from the alkene VI and 5α-pregnane had identical structures.

Table II
Metastable Defocusing Results for the *m/e* 218 Ion

Compd	[218 → 203]/[218 → 189]	[218 → 175]/[218 → 148]	[218 → 189]/[218 → 175]
5α-Pregnane (I)	19	0.49	0.07
$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrostene (VI)	15	0.56	0.06
$\Delta^{13(14)}$-13,17-Seco-5α-*D*-homoandrostene (VII)	13	0.50	0.05
5α-Androstane-13,17-seco-17-oic acid lactone (XXI)	13	0.75	0.06
5α-*D*-homoandrostane	3.5	2.5	1.0

Four first field-free region metastable transitions arising from the *m/e* 218 ion were utilized in these experiments. The reactions corresponded to loss of CH_3 (218 → 203), loss of C_2H_5 (218 → 189), loss of C_3H_7 (218 → 175), and loss of C_5H_{10} (218 → 148). The intensity ratios[20] of metastables arising from the *m/e* 218 ions of 5α-pregnane, of 5α-androstane-13,17-seco-17-oic acid (eq 7), and of the exocyclic alkene VI agreed closely (Table II), consistent with their structural identity. In contrast, the ratios observed from the *m/e* 218 ion of *D*-homoandrostane were markedly different. This is not unexpected, since it has been demonstrated that these ions arise largely (ca. 70%) from ring A cleavage (eq 8).[7] The widely divergent ratios observed, however, demonstrate that the technique has utility for establishing the structure of steroid ions.

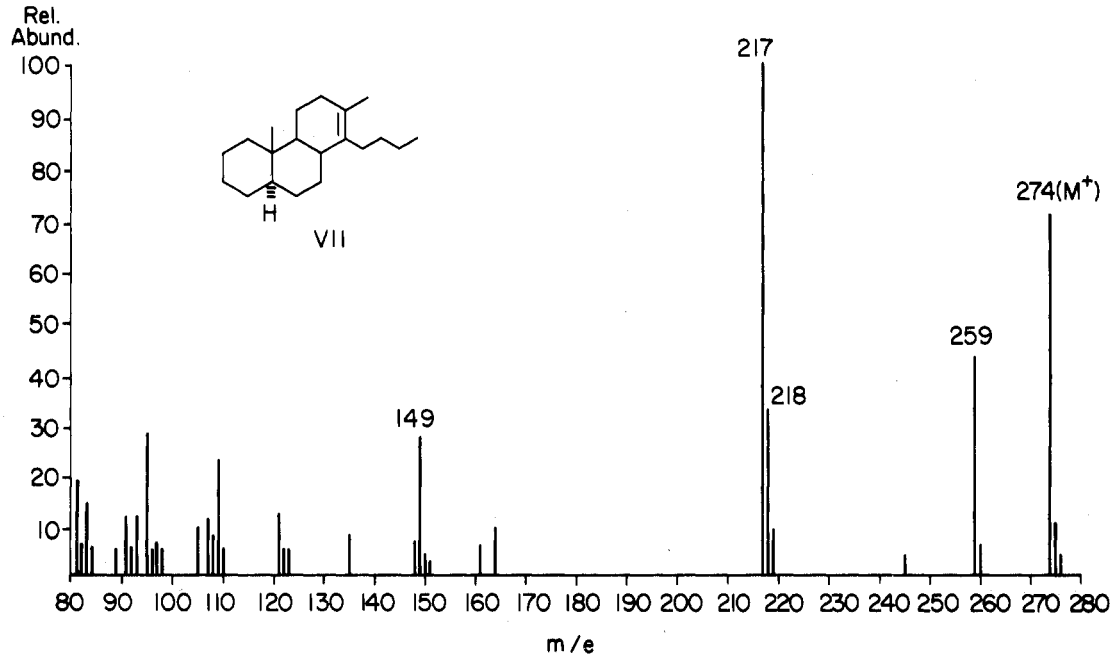
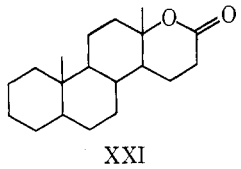


Figure 2.

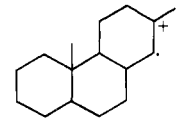
Table III
Shifts[a] of Peaks Corresponding to Ring D in $\Delta^{13(14)}$-13,17-Seco-5α-*D*-homoandrostene (VII)

Compd	Isotopic purity, %	M⁻	M − C_4H_8	M − C_4H_9
$-d_0$		274	218	217
-17a,17a,17a-d_3	d_3 95	277	218	217
-17,17-d_2	d_2 97	276	218	217
-16,16-d_2	d_2 97	276	219	217

[a] Reported shifts are corrected for isotopic impurity as well as ^{13}C contributions and are greater than 95% unless otherwise indicated.

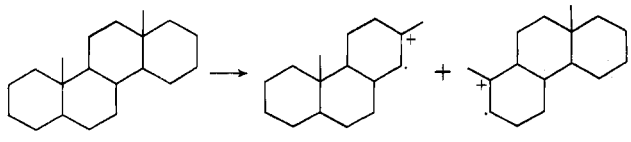


XXI



+ CO_2 + C_2H_4 (7)

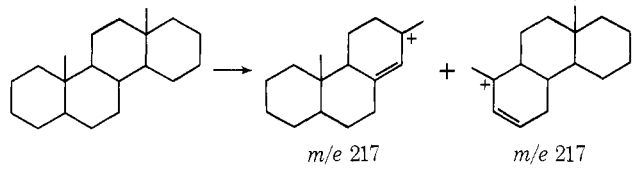
m/e 218



m/e 218 (30%) *m/e* 218 (70%)

(8)

Ionization of $\Delta^{13(14)}$-13,17-seco-*D*-homoandrostene (VII) and charge localization in the carbon–carbon double bond generates b; according to Scheme I, b fragments to give *m/e* 217. Inspection of Figure 2 indicates that the base peak in the spectrum of the $\Delta^{13(14)}$ alkene is indeed at *m/e* 217. Deuterium-labeling experiments (Table III) demonstrated that labels at C-17a, C-17, and C-16 were completely eliminated, as the mechanism of Scheme I predicts. In an effort to determine whether the *m/e* 217 ion from VII and that of 5α-pregnane were identical, the intensities of two first field-free region metastables [loss of C_4H_7 (217 → 162) and loss of C_5H_8 (217 → 149)] were determined. The ratio of their intensities (Table III) was nearly identical for the *m/e* 217 ions of pregnane and of the $\Delta^{13(14)}$ alkene, consistent with their structural identity. In contrast, the intensity ratio for metastables arising from the *m/e* 217 ion of *D*-homoandrostane (known[7] to be largely isomeric, eq 9) dif-

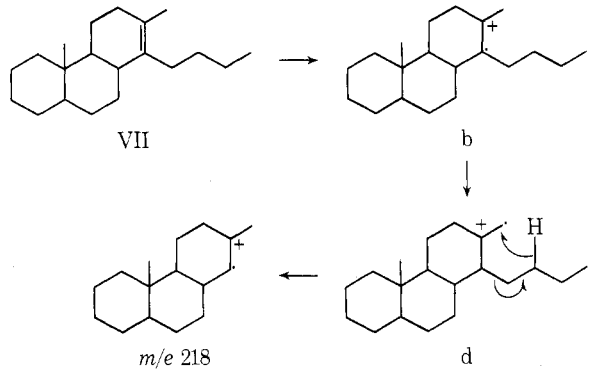


m/e 217 *m/e* 217

(9)

fered by an order of magnitude, confirming the sensitivity of these ratios to steroid structure.

A troubling aspect of the mechanism of Scheme I is the small amount (<10%) of interconversion of ions b and d.[21] In this connection, it is interesting to note that the spectrum of the $\Delta^{13(14)}$ alkene (VII) exhibits a significant peak at *m/e* 218 (217/218 = 6.95). A priori, the *m/e* 218 ion could arise either by isomerization of b to d followed by the usual fragmentation process, or it could form through direct fragmentation of b. Considerable evidence points to its origin by the isomerization pathway. Metastable defocusing data (Table II) are consistent with structural identity between the *m/e* 218 ion of the $\Delta^{13(14)}$ alkene and that of 5α-pregnane. Further, deuterium-labeling experiments (Table III) establish that the genesis of the *m/e* 218 involves migration



VII b

(10)

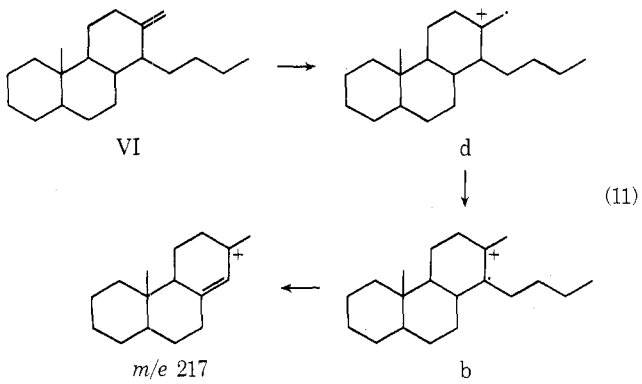
m/e 218 d

Table IV
Metastable Defocusing Results for the *m/e* 217 Ion

Compd	[217 → 162]/[217 → 149]
5α-Pregnane (I)	1.9
$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrostene (VI)	1.6
$\Delta^{13(14)}$-13,17-Seco-5α-*D*-homoandrostene (VII)	1.8
5α-*D*-Homoandrostane	0.11

of a hydrogen from C-16, again consistent with behavior already observed for d (cf. eq 10).

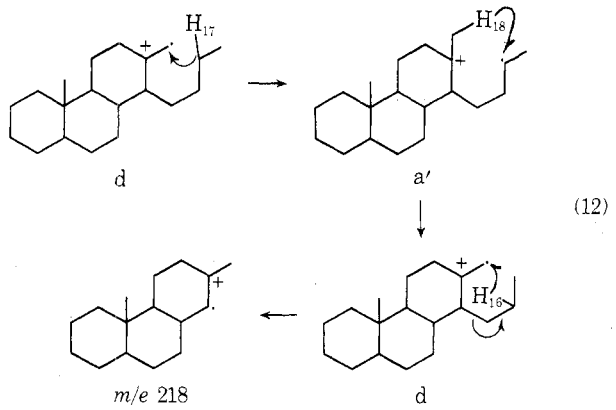
Similarly, the mass spectrum of the $\Delta^{13(18)}$ alkene VI exhibits a significant peak at *m/e* 217 (217/218 = 0.34). Again, it appears likely that an isomerization reaction is occurring to produce *m/e* 217. Metastable data (Table IV) are consistent with a common structure for the *m/e* 217 ions from 5α-pregnane and from the $\Delta^{13(18)}$ alkene. Deuterium-labeling experiments (Table I) demonstrate that the genesis of the *m/e* 217 ion involves predominant expulsion of C-16, C-17, and C-17a hydrogens, consistent with behavior already described for d (cf. eq 11). Thus, the interconver-



(11)

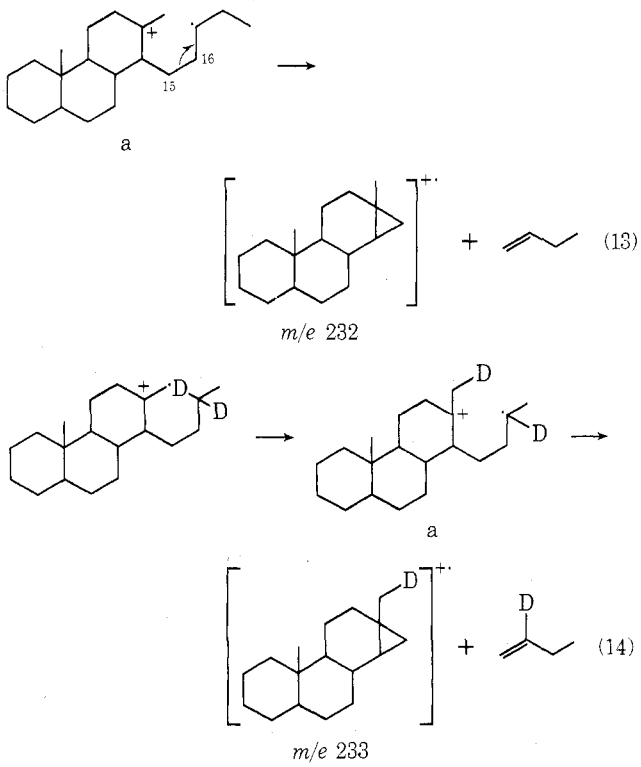
sion reactions b → d and d → b are more significant for the *m/e* 218 and 217 ions generated from the alkenes VI and VII than for the corresponding ions generated from intact steroids. The modest differences observed, however, are probably attributable to differences in the internal energies of the ions generated from the different sources, rather than structural differences.[22]

The mechanisms of the isomerization reactions remain obscure, but a related observation merits comment. The labeling data (Table I) require that the genesis of *m/e* 218 in the spectrum of $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostane (VI) always involves transfer of a hydrogen atom from C-16. Nevertheless, a 20% transfer from C-17 also occurs. An attractive rationalization of this phenomenon is depicted in eq 12. Transfer of a hydrogen atom from C-17 gener-



(12)

ates a', analogous to the ion formed by charge localization in the C-13–C-17 bond of 5α-pregnane. Reciprocal transfer of a C-18 hydrogen regenerates d, which can fragment in the usual way to produce *m/e* 218. Supporting this hypothesis is the observation that the *m/e* 232 peak shifts cleanly to *m/e* 233 in the spectrum of the 17,17-dideuterated $\Delta^{13(18)}$ alkene. The *m/e* 232 peak in steroids such as 5α-cholestane arises via cleavage of the C-15–C-16 bond of the initially formed ion a (eq 13).[2] If the *m/e* 232 ion in the mass spectrum of the $\Delta^{13(18)}$ alkene is arising by an analogous process, a shift to *m/e* 233 is predicted on deuteration of the 17 position (eq 14). It is notable that the *m/e* 232



(13)

(14)

peak is absent from the spectrum of the $\Delta^{13(14)}$ alkene, suggesting that conversion of b to a' does not occur.

Conclusions

The results obtained here provide strong evidence in support of the mechanism depicted in Scheme I for the characteristic ring D fragmentation of steroids. Deuterium-labeling experiments established that b and d, generated via alternative pathways, do, in fact, fragment as predicted. Metastable defocusing studies were consistent with identical structures for the *m/e* 218 ions generated from the $\Delta^{13(18)}$ alkene and from 5α-pregnane.

Evidence was obtained for a significant amount of isomerization of ions b and d, when generated by direct electron impact, and evidence for the reversibility of the initial hydrogen abstraction from C-18 (a → d) was observed.

The most useful result obtained from these studies, however, relates to the demonstrated sensitivity of metastable abundance ratios to steroid ion structure. These results suggest that the defocusing technique may have wide application to the solution of mechanistic and structural problems in steroid mass spectrometry.

Experimental Section

Melting points are uncorrected. Infrared spectra were measured on a Beckman IR-10 spectrometer in chloroform solution. NMR spectra were recorded on a Varian A-60A spectrometer or a Varian HA-100D spectrometer interfaced with a Digilab FTS-3 Fourier transform data system. All NMR spectra were run in deuteriochloroform solution with tetramethylsilane as a internal reference. Optical rotations were measured on dilute solutions in chloroform. All mass spectra were run on an AEI-MS 902 spectrometer at 70 eV

using the direct inlet procedure. Thin layer chromatography was carried out on silica gel (HF-254). All reactions were run under nitrogen unless otherwise specified.

$\Delta^{13(18)}$-13,17-Seco-5α-androstene-17-nitrile (IX). 5α-Androstan-17-one oxime[14,23] (VIII, 1.5 g, 5.17 mmol) was dissolved in 10 ml of dry pyridine. *p*-Toluenesulfonyl chloride (1.5 g, 7.84 mmol) was added and the reaction mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with 120 ml of ice water and extracted into chloroform. The extracts were washed twice with 10% hydrochloric acid to remove all the pyridine. Column chromatography on silica gel (benzene, benzene–methylene chloride) yielded 0.680 g (2.35 mmol, 45.6% yield, ~20% conversion) of 13α-amino-13,17-seco-5α-androstan-17-oic acid lactam[14] (mp 311–313°) and 0.735 g (2.61 mmol, 52.5% yield, ~20% conversion) of $\Delta^{13(18)}$-13,17-seco-5α-androstene-17-nitrile (IX):[24] mp 57–62°; ν_{max} 2248 (–C≡N) and 1647 cm^{-1} (>C=); NMR C-19 CH_3 0.70 (singlet), $-CH_2CN$ 2.35 (triplet), olefinic protons 4.52 (singlet) and 4.83 ppm (singlet); $[\alpha]^{25}D$ −34.6°. Anal. Calcd for $C_{19}H_{29}N$: mol wt, 271.2300. Found: mol wt, 271.2306.

$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-one (X). $\Delta^{13(18)}$-13,17-Seco-5α-androstene-17-nitrile (IX, 148 mg, 0.545 mmol) was dissolved in 40 ml of dry ether. Methyllithium (34 mmol, Ventron, 1.8 *M* in ether) was added dropwise to the ice-cooled reaction flask. The reaction mixture was allowed to warm to room temperature over a 3-hr period, at which time it was quenched with a saturated ammonium chloride solution. The mixture was extracted with ether and washed twice with water. After drying over magnesium sulfate and purification by thin layer chromatography on silica gel (chloroform) a colorless oil, $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-one, was obtained (X, 143 mg, 0.49 mmol, 90%): ν_{max} 1710 (C=O), 1640 cm^{-1} (>C=); NMR C-19 CH_3 0.71 (singlet), CH_3C=O 2.13 (singlet), $-CH_2C$=O 2.4 (multiplet), and olefinic protons at 4.5 (singlet) and 4.74 ppm (singlet); $[\alpha]^{25}D$ −25.2°. Anal. Calcd for $C_{20}H_{32}O$: mol wt, 288.2453. Found: mol wt, 288.2446.

$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-ol (XI). Lithium aluminum hydride (100 mg, 2.62 mmol) was added to 35 ml of dry ether and the mixture was brought to reflux. $\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-one (X, 45 mg, 0.155 mmol) dissolved in 20 ml of dry ether was added dropwise to the refluxing mixture. Refluxing was continued for 3 hr, at which time the mixture was quenched with a saturated ammonium chloride solution. The mixture was filtered hot to remove the lithium salts. The filtrate was then extracted with ether and washed with water. After drying over magnesium sulfate the mixture was purified by thin layer chromatography on silica gel and eluted with chloroform. This yielded 32 mg (0.109 mmol, 70%) of the colorless oil $\Delta^{13(18)}$-13,17-seco-5α-*D*-homandrosten-17-ol (XI): ν_{max} 3610 (–OH), 1647 cm^{-1} (>C=); NMR C-19 CH_3 0.63 (singlet), olefinic protons 4.50 (singlet), 4.62 ppm (singlet). Anal. Calcd for $C_{20}H_{34}O$: mol wt, 290.2609. Found: mol wt, 290.2607.

$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-ol Tosylate (XII). $\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-ol (XI, 8.5 mg, 0.03 mmol) was dissolved in 3 ml of dry pyridine and cooled in ice for 0.5 hr. *p*-Toluenesulfonyl chloride (10 mg, 0.052 mmol) was then added and the reaction mixture was kept at ~10° for 24 hr. The reaction mixture was then quenched with ice–water and extracted into ether, washed twice with water, and dried over magnesium sulfate. Thin layer chromatography on silica gel (cyclohexane–toluene) yielded 10 mg (0.023 mmol, 77%) of the colorless oil $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-ol tosylate (XII): ν_{max} 1350, 1170 ($-SO_2$), and 1647 cm^{-1} (>C=); NMR C-19 CH_3 0.60 (singlet), tolyl methyl 2.33 (singlet), aromatic protons 7.2–7.71, olefinic protons 4.30 (singlet), 4.55 ppm (singlet).

$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrostene (VI). Lithium aluminum hydride (100 mg, 2.62 mmol) was added to 35 ml of freshly distilled tetrahydrofuran and the mixture was brought to reflux. $\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-ol tosylate (XII, 10 mg, 0.023 mol) dissolved in 15 ml of tetrahydrofuran was added dropwise to the refluxing mixture. Refluxing was continued for 3 hr. The mixture was then quenched with a saturated ammonium chloride solution. The hot solution was filtered and the filtrate was extracted with ether and washed twice with water. After drying over magnesium sulfate, purification by chromatography on silica gel (pentane) yielded 4.62 mg (0.0168 mmol, 73%) of the colorless oil $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene (VI): ν_{max} 1647 cm^{-1} (>C=); NMR C-19 CH_3 0.70 (singlet), olefinic protons at 4.55 (singlet) and 4.68 ppm (singlet); $[\alpha]^{25}D$ −15.5°. Anal. Calcd for $C_{20}H_{34}$: mol wt, 274.2660. Found: mol wt, 274.2665.

$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrostene-*17,17-d*$_2$ (XVII). Lithium aluminum deuteride (104 mg, 2.62 mmol) was added to 35 ml of dry ether and the mixture was brought to reflux. $\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-one (X, 45 mg, 0.155 mmol) dissolved in 20 ml of dry ether was added dropwise to the refluxing mixture. Refluxing was continued for 3 hr, at which time the mixture was quenched with a saturated ammonium chloride solution. The mixture was filtered hot to remove the lithium salts and the filtrate was extracted into ether and washed with water. After drying over magnesium sulfate the mixture was thin layer chromatographed on silica gel and eluted with chloroform to give 32.6 mg (0.112 mmol, 72%) of the colorless oil $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-ol-*17-d*$_1$ (XV). Its NMR and ir spectra were identical with those of the unlabeled compound XI. The $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-ol tosylate-*17-d*$_1$ (XVI) was prepared from $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-ol-*17-d*$_1$ (XV) in a manner analogous to the preparation of the unlabeled tosylate XII. Lithium aluminum deuteride (104 mg, 2.62 mmol) was added to 35 ml of freshly distilled tetrahydrofuran and the mixture was brought to reflux. $\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-ol tosylate-*17-d*$_1$ (XVI, 11 mg, 0.0247 mol) dissolved in 15 ml of distilled tetrahydrofuran was added dropwise to the refluxing mixture. Refluxing was continued for 3 hr and then the mixture was quenched with a saturated ammonium chloride solution. Work-up was analogous to that of the unlabeled hydrocarbon VI. Thin layer chromatography yielded 5.35 mg (0.0193 mol, 78%) of the colorless oil $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene-*17,17-d*$_2$ (XVII). The ir spectrum was identical with that of the unlabeled analog. The NMR spectrum was similar; however, the terminal side-chain methyl (C-17a) was apparent at 0.90 ppm as a broad singlet. Mass spectroscopy gave a molecular ion at *m/e* 276 (96% d_2).

$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrostene-*17a,17a,17a-d*$_3$ (XVI). To a thoroughly dried flask was added 645 mg (92.4 mmol) of benzene-washed lithium metal cut into 1-cm pieces. The lithium was stirred in 40 ml of anhydrous ether under argon. To this mixture was added 6.9 g (47.4 mmol) of methyl iodide-d_3 dropwise.[25] The reaction mixture was refluxed for 1 hr and then stored under argon until needed. Titration showed the methyllithium-d_3 to be 0.8 *M*. $\Delta^{13(18)}$-13,17-Seco-5α-androstene-17-nitrile (IX, 148 mg, 0.545 mmol) was dissolved in 40 ml of dry ether and stirred under argon. Methyllithium-d_3 prepared as above (4.25 ml, 34 mmol) was added dropwise to the ice-cooled reaction flask. After 3 hr at room temperature the reaction was quenched with saturated ammonium chloride solution. Work-up and purification was identical with that of the unlabeled ketone X. A colorless oil, $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-one-*17a,17a,17a-d*$_3$ was obtained (XIII, 146 mg, 0.502 mmol, 92%). Its ir spectrum was identical with that of the unlabeled ketone X and its NMR spectrum was similar except for the absence of the ketone α-methyl group at 2.13 ppm. The conversion of the $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-one-*17a,17a,17a-d*$_3$ (XIII) to the corresponding trideuterated alcohol, tosylate, and hydrocarbon are identical with those of the unlabeled derivatives already described. The $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene-*17a,17a,17a-d*$_3$ (XIV) had ir and NMR spectra identical with that of the unlabeled hydrocarbon VI. The mass spectrum had a molecular ion at *m/e* 277 (63% d_3).

$\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrostene-*16,16,17a,17a,17a-d*$_5$ (XIX). $\Delta^{13(18)}$-13,17-Seco-5α-*D*-homoandrosten-17-one (X, 37 mg, 0.128 mmol) was dissolved in 5 ml of methanol-d_3. Deuterium oxide (2 ml) was added and the solution was refluxed with 100 mg of anhydrous potassium carbonate. After 48 hr the procedure was repeated with fresh methanol-d_3 and deuterium oxide. Extraction into chloroform and evaporation of the solvent yielded $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-one-*16,16,17a,17a,17a-d*$_5$ (XVIII). Its ir spectrum was identical with that of the unlabeled ketone X. Its NMR appeared identical except for the absence of all ketonic protons at 2.9 and 2.13 ppm. The mass spectrum showed a molecular ion at *m/e* 293. The conversion of the $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrosten-17-one-*16,16,17a,17a,17a-d*$_5$ (XVIII) to its corresponding alcohol, tosylate, and hydrocarbon is identical with that of the unlabeled derivatives already described. The $\Delta^{13(18)}$-13,17-seco-5α-*D*-homoandrostene-*16,16,17a,17a,17a-d*$_5$ (XIX) had ir and NMR spectra identical with those of the unlabeled hydrocarbon VI. The mass spectrum had a molecular ion at *m/e* 279 (89% d_5).

5α-Androstane-13,17-seco-17-oic Acid Lactone (XXI). Hydrogen peroxide (90%, 0.5 ml, 22 mmol) was added to 3 ml of methylene chloride. Trifluoroacetic anhydride (1 ml, 5.25 mmol) was added slowly to the ice-cooled mixture. After stirring for 0.5 hr the peracid was added slowly to an ice-cooled solution of 1 g (3.65

mmol) of 5α-androsten-17-one (XX)[16] dissolved in 10 ml of methylene chloride. The reaction was allowed to proceed overnight, when the mixture was diluted with water and extracted into methylene chloride. The extracts were washed twice with a 10% sodium carbonate solution and the solvent was evaporated. Recrystallization from ethanol yielded a white, crystalline solid (mp 227–230°) of 5α-androstane-13,17-seco-17-oic acid lactone (XXI, 825 mg, 2.84 mmol, 78%).[17]

13,17-Seco-5α-androstane-13α,17-diol (XXII). Lithium aluminum hydride (200 mg, 5.24 mmol) was added to 50 ml of freshly distilled dioxane and the mixture was brought to reflux. A solution of 5α-androstane-13,17-seco-17-oic acid lactone (XXI, 825 mg, 2.84 mmol) in 50 ml of freshly distilled dioxane was added dropwise to the refluxing mixture. Refluxing was continued for 15 hr, at which time the reaction was quenched with a saturated ammonium chloride solution. The mixture was filtered to remove the lithium salts and the filtrate was extracted into chloroform, washed twice with 5% hydrochloric acid, and dried over magnesium sulfate. Recrystallization from ethanol–2% water yielded 664 mg (2.26 mmol, 80%) of white crystals of 13,17-seco-5α-androstane-13α,17-diol (XXII, mp 149.5–150.5°): ν_{max} 3600–3320 (broad, OH), 1120 (tertiary OH), 1050 cm^{-1} (primary OH); NMR C-18 CH_3 1.1 (singlet), C-19 CH_3 0.73 (singlet), C-17a CH_2OH 3.63 ppm (triplet); $[\alpha]^{25}D$ +5.17°. Anal. Calcd for $C_{19}H_{34}O_2$: mol wt, 294.2561. Found: mol wt, 294.2569.

13,17-Seco-5α-androstane 13α,17-Diacetate (XXIII). 13,17-Seco-5α-androstane-13α,17-diol (XXII, 317 mg, 1.08 mmol) was dissolved in 10 ml of dry pyridine. Acetic anhydride (500 mg, 4.8 mmol) was added and the mixture was heated at 70° for 24 hr. The reaction mixture was diluted with water and extracted into chloroform. Two washes with 5% hydrochloric acid removed the last traces of pyridine. After column chromatography on silica gel (Woelm) and elution with benzene followed by chloroform, 303 mg (0.80 mmol, 74%) of a colorless oil, 13,17-seco-5α-androstane 13α,17-diacetate (XXIII), was isolated: ν_{max} 1725 cm^{-1} (O=$COCH_3$); NMR C-18 CH_3 1.36 (singlet), C-19 CH_3 0.71 (singlet), C-13 OC(=O)CH_3 2.01 (singlet), C-17 OC(=O)CH_3 1.94 (singlet), C-17 (CH_2OC=O) 4.0 ppm (triplet); $[\alpha]^{25}D$ +20.14°. The mass spectrum gave no molecular ion but the base peak was at *m/e* 318 (M^+ − AcOH), consistent with a tertiary acetate.

$\Delta^{13(14)}$-13,17-Seco-5α-androstene 17-Acetate (XXXI). 13,17-Seco-5α-androstane 13α,17-diacetate (XXIII, 78 mg, 0.206 mmol) was placed in a sublimation tube equipped with a Dry Ice–acetone cooled cold finger. The sublimator was flushed with nitrogen and placed in an oil bath (preheated to 332°) for 10 min. The product was purified by thin layer chromatography on silica gel (chloroform) to give a mixture of three isomeric olefins. The exocyclic olefin, $\Delta^{13(18)}$-13,17-seco-5α-androstene 17-acetate (XXIV), was removed by careful chromatography on silica gel impregnated with 10% silver nitrate[18] (benzene–2.5% acetone). The remaining mixture[26] contained 43 mg (0.113 mmol, 55%) of the colorless oil $\Delta^{13(14)}$-13,17-seco-5α-androstene 17-acetate (XXXI): ν_{max} 1730 (O=CCH_3), 1660 cm^{-1} (weak, >C=C<); NMR C-18 CH_3 1.59 (singlet), C-19 CH_3 0.72 (singlet), C-17 OC(=O)CH_3 2.02 (singlet), C-17 (CH_2OC=O) 4.01 ppm (triplet). The small peak at 5.5 ppm was due to the $\Delta^{12(13)}$ double bond isomer. Anal. Calcd for $C_{21}H_{34}O_2$: mol wt, 318.2559. Found: mol wt, 318.2557.

$\Delta^{13(14)}$-13,17-Seco-5α-androsten-17-ol (XXXII). The isomeric mixture $\Delta^{13(14)}$- and $\Delta^{12(13)}$-13,17-seco-5α-androstene 17-acetate (75 mg, 0.236 mmol) was dissolved in 20 ml of methanol. Water (2 ml) and potassium hydroxide (ca. 450 mg) were added and the mixture was refluxed for 0.5 hr. The mixture was diluted with water and extracted into chloroform. After washing with 10% hydrochloric acid and drying over magnesium sulfate the mixture was purified by thin layer chromatography on silica gel (chloroform) to give 55 mg (0.199 mmol, 84%) of the isomeric $\Delta^{12(13)}$- and $\Delta^{13(14)}$-13,17-seco-5α-androsten-17-ol (XXVI and XXXII): ν_{max} 3600–3300 cm^{-1} (broad, primary –OH); NMR C-18 CH_3 1.59 (singlet), C-19 CH_3 0.73 (singlet), C-17 CH_2OH 3.6 ppm (triplet). The small peak at 5.5 ppm was due to the $\Delta^{12(13)}$ isomer (XXVI). Anal. Calcd for $C_{19}H_{32}O$: mol wt, 276.2453. Found: mol wt 276.2459.

$\Delta^{13(14)}$-13,17-Seco-5α-androsten-17-ol Tosylate (XXXIII). The isomeric mixture of $\Delta^{13(14)}$- and $\Delta^{12(13)}$-13,17-seco-5α-androsten-17-ol (XXXII and XXVI, 42 mg, 0.152 mmol) was dissolved in 10 ml of dry pyridine and chilled to 0°. The flask was then flushed with nitrogen and 100 mg (0.502 mmol) of *p*-toluenesulfonyl chloride was added. The flask was kept at 10° for 18 hr and then diluted with 120 ml of water. Extraction into chloroform was followed by two washes with 5% hydrochloric acid to remove all the pyridine. Thin layer chromatography on silica gel (chloroform) yielded 44 mg (0.102 mmol, 67%) of the isomeric $\Delta^{12(13)}$- and $\Delta^{13(14)}$-13,17-seco-5α-androsten-17-ol tosylate (XXVII and XXXIII): ν_{max} 1350, 1170 cm^{-1} (SO_2): NMR C-18 CH_3 1.57 (singlet), C-19 CH_3 0.70 (singlet), tolyl CH_3 2.44 (singlet), aromatic protons 7.20–7.71 ppm. The small peak at 5.5 ppm was due to the $\Delta^{12(13)}$ isomer.

17-Iodo-$\Delta^{13(14)}$-13,17-seco-5α-androstene (XXXIV). The isomer mixture of $\Delta^{12(13)}$- and $\Delta^{13(14)}$-13,17-seco-5α-androsten-17-ol tosylate (XXVII and XXXIII, 44 mg, 0.102 mmol) was dissolved in 10 ml of acetone. Sodium iodide (30.6 mg, 0.204 mmol) was added and the reaction flask was placed in the dark under nitrogen. After a few hours white crystals of sodium tosylate started to precipitate out. The reaction was allowed to proceed until the formation of new crystals ceased (ca. 30 hr). Dilution with water and extraction into chloroform followed by thin layer chromatography on silica gel (benzene) yielded 12 mg (0.031 mmol, 56%) of the isomeric 17-iodo-$\Delta^{12(13)}$- and -$\Delta^{13(14)}$-13,17-seco-5α-androstene (XXVIII and XXXIV): no significant ir absorptions; NMR C-18 CH_3 1.62 (singlet), C-19 CH_3 0.72 (singlet), C-17 CH_2I 3.18 ppm (triplet). Anal. Calcd for $C_{19}H_{31}I$: mol wt, 386.1474. Found: mol wt, 386.1468.

$\Delta^{13(14)}$-13,17-Seco-5α-*D*-homoandrostene (VII). Copper iodide (156 mg, 0.816 mmol, Alfa Inorganics Ultra Pure) was added to a thoroughly dried three-necked flask containing 3 ml of anhydrous ether. While this mixture was stirring at −10° (ice–acetone) 2.6 ml of methyllithium (1.63 mmoles, 0.63 *M*) in ether (prepared from 0.5 mol of lithium metal and 0.25 mol of methyl iodide)[25] was added dropwise. The first few drops of methyllithium generated a bright yellow color which became a light tan color on complete addition of the methyllithium.[27] The lithium dimethylcopper was allowed to stir for 0.5 hr at −10°, at which time 24 mg (0.0623 mmol) of the isomeric 17-iodo-$\Delta^{12(13)}$- and -$\Delta^{13(14)}$-13,17-seco-5α-androstene (XXVIII and XXXIV) dissolved in 5 ml of anhydrous ether was added dropwise. This mixture was stirred at −10° for 6 hr and then quenched with water and extracted into ether. Repeated water washes, drying over magnesium sulfate, and thin layer chromatography on silica gel (pentane) gave the isomeric mixture of $\Delta^{12(13)}$- and $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene (XXIX and VII). Careful chromatography on 10% silver nitrate impregnated silica gel[18] (hexane–6.5% benzene) yielded 9.3 mg (0.034 mmol, 55%) of the pure, colorless oil $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene (VII): ν_{max} 2920, 2860 (C–H), 1660 cm^{-1} (weak, >C=C<); NMR C-18 CH_3 1.62 (singlet), C-19 CH_3 0.72 ppm (singlet) (the small peak at 5.5 ppm is absent); $[\alpha]^{25}D$ −60°. Anal. Calcd for $C_{20}H_{34}$: mol wt, 274.2661. Found: mol wt, 274.2660.

$\Delta^{13(14)}$-13,17-Seco-5α-*D*-homoandrostene-*17a,17a,17a-d*$_3$ (XXXV). The isomeric mixture of 17-iodo-$\Delta^{12(13)}$- and -$\Delta^{13(14)}$-13,17-seco-5α-androstene (XXVIII and XXXIV, 24 mg, 0.0623 mmol) was treated in a similar manner as above except that methyl iodide-d_3 was substituted for methyl iodide in the preparation of the methyllithium-d_3.[25] Silica gel (pentane) thin layer chromatography followed by silica gel–10% silver nitrate[18] (hexane–6.5% benzene) thin layer chromatography yielded the isomerically pure, colorless oil $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene-*17a,17a,17a-d*$_3$ (XXXV, 10.0 mg, 0.037 mmol, 59%). Its ir and NMR spectra were identical with those of the unlabeled analog VII. Its mass spectrum had a molecular ion at *m/e* 277 (95% d_3).

$\Delta^{13(14)}$-13,17-Seco-5α-*D*-homoandrostene-*16,16-d*$_2$ (XXXVII). 5α-Androsten-17-one (XX, 921 mg, 3.35 mmol) was dissolved in 10 ml of methanol-d_1. Anhydrous potassium carbonate (200 mg) and 2 ml of deuterium oxide was added and the mixture was refluxed for 48 hr. The process was repeated with fresh methanol-d_1 and deuterium oxide. The reaction mixture was then diluted with water and extracted into chloroform. Its ir spectrum was identical with that of the unlabeled ketone XX (mp 114–116°).[16] Its NMR spectrum was similar to that of the unlabeled ketone XX except for the absence of the ketonic methylene protons at 2.28 ppm. The mass spectrum showed a molecular ion at *m/e* 276. The conversion of 5α-androstan-17-one-*16,16-d*$_2$ to the corresponding $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene-*16,16-d*$_2$ (XXXVII) was accomplished in the usual manner. The $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene-*16,16-d*$_2$ (XXXVII) had ir and NMR spectra identical with those of the unlabeled hydrocarbon VII. Its mass spectrum showed a molecular ion at *m/e* 276 (97% d_2).

$\Delta^{13(14)}$-13,17-Seco-5α-*D*-homoandrostene-*17,17-d*$_2$ (XXXVI). 5α-Androstane-13,17-seco-17-oic acid lactone (XXI, 825 mg, 2.84 mmol) dissolved in 50 ml of freshly distilled dioxane was added dropwise to a refluxing mixture of 190 mg (5 mmol) of lithium aluminum deuteride in 50 ml of freshly distilled dioxane. The mixture was refluxed for 18 hr and then quenched with a saturated ammonium chloride solution. Filtration removed the lithium salts and

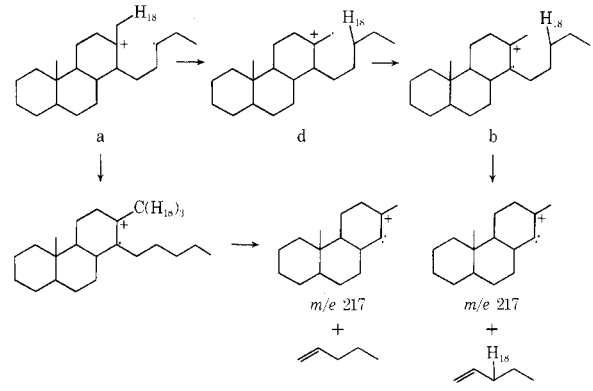
then the filtrate was extracted into chloroform. Thin layer chromatography on silica gel (chloroform) yielded 712 mg (2.41 mmol, 85%) of white crystalline 13,17-seco-5α-androstene-13α,17-diol-*17,17-d*$_2$ (mp 148–150°). Its ir spectrum was identical with that of the unlabeled diol XXII. Its NMR spectrum was similar except for the absence of the C-17 methylene protons at 3.63 ppm. The mass spectrum showed a molecular ion at *m/e* 296. The conversion of 13,17-seco-5α-androstane-13α,17-diol-*17,17-d*$_2$ to the corresponding $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene-*17,17-d*$_2$ (XXXVI) was accomplished in the usual manner.

The $\Delta^{13(14)}$-13,17-seco-5α-*D*-homoandrostene-*17,17-d*$_2$ (XXXVI) had an ir spectrum identical with that of the unlabeled hydrocarbon VII. Its NMR spectrum was similar except that the terminal C-17a methyl group appeared at 0.90 ppm as a broad signal. The mass spectrum showed a molecular ion at *m/e* 276 (97% d_2).

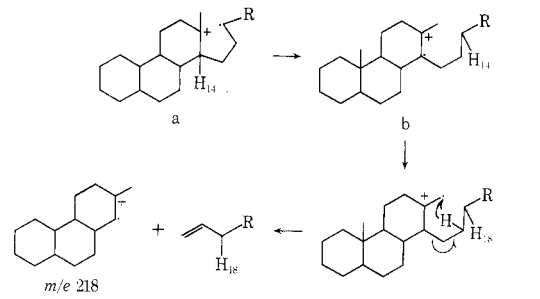
Registry No.—VI, 54869-94-2; VII, 54869-95-3; VIII, 1035-62-7; IX, 22214-86-4; X, 54869-96-4; XI, 54869-97-5; XII, 54869-98-6; XIII, 54869-99-7; XIV, 54870-00-7; XV, 54870-01-8; XVI, 54870-02-9; XVII, 54911-57-8; XVIII, 54870-03-0; XIX, 54870-04-1; XX, 963-74-6; XXI, 2466-25-3; XXII, 54870-05-2; XXIII, 54870-06-3; XXIV, 54870-07-4; XXV, 54870-08-5; XXVI, 54870-09-6; XXVII, 54870-10-9; XXVIII, 54870-11-0; XXIX, 54870-12-1; XXXI, 54870-13-2; XXXII, 54870-14-3; XXXIII, 54870-15-4; XXXIV, 54870-16-5; XXXV, 54910-88-2; XXXVI, 54933-60-7; XXXVII, 54933-61-8; 13, 17-seco-5α-androstane-13α, 17-diol-*17, 17-d*$_2$, 54870-17-6.

References and Notes

(1) We are indebted to the National Institutes of Health for financial assistance (Grant GM 20003-01).
(2) L. Tökés, G. Jones, and C. Djerassi, *J. Am. Chem. Soc.*, **90**, 5465 (1968).
(3) R. I. Reed, *J. Chem. Soc.*, 3432 (1958).
(4) S. S. Friedland, G. H. Lane, R. T. Longman, K. E. Train, and M. J. O'Neal, Jr., *Anal. Chem.*, **31**, 169 (1959); H. M. Fitches, *Adv. Mass Spectrom.*, **2**, 431 (1962).
(5) R. Ryhage and E. Stenhagen, *J. Lipid Res.*, **1**, 361 (1960).
(6) L. Tökés and C. Djerassi, *J. Am. Chem. Soc.*, **91**, 5017 (1969).
(7) G. Eadon, S. Popov, and C. Djerassi, *J. Am. Chem. Soc.*, **94**, 282 (1972).
(8) R. R. Muccino and C. Djerassi, *J. Am. Chem. Soc.*, **96**, 556 (1974).
(9) See, for example, H. Fritz, H. Budzikiewicz, and C. Djerassi, *Chem. Ber.*, **99**, 35 (1966); H. Budzikiewicz, C. Fenselau, and C. Djerassi, *Tetrahedron*, **22**, 1391 (1966).
(10) K. K. Mayer and C. Djerassi, *Org. Mass Spectrom.*, **5**, 817 (1971); T. H. Kinstle and R. E. Stark, *J. Org. Chem.*, **32**, 1318 (1967); D. S. Weinberg and C. Djerassi, *ibid.*, **31**, 115 (1966); B. J. Millard and D. F. Shaw, *J. Chem. Soc. B*, 664 (1966).
(11) M. Spiteller-Friedmann, S. Eggers, and G. Spiteller, *Monatsh. Chem.*, **95**, 1740 (1964); C. C. Fenselau and F. P. Abramson, *Org. Mass Spectrom.*, **2**, 915 (1969).
(12) I. Howe and D. H. Williams, *J. Am. Chem. Soc.*, **90**, 5461 (1968); A. Mandelbaum and K. Biemann, *ibid.*, **90**, 2975 (1968); H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, San Francisco, Calif., 1967, Chapter 1.
(13) S. G. Wyllie and C. Djerassi, *J. Org. Chem.*, **33**, 305 (1968); M. Kraft and G. Spiteller, *Org. Mass Spectrom.*, **2**, 865 (1969); M. T. Praet, *ibid.*, **4**, 65 (1970); Y. M. Sheikh and C. Djerassi, *J. Org. Chem.*, **38**, 3545 (1973).
(14) A. Cervantes, P. Crabbé, J. Iriarte, and G. Rosenkranz, *J. Org. Chem.*, **33**, 4294 (1968).
(15) D. H. R. Barton, J. P. Poyser, and P. G. Sommes, *J. Chem. Soc., Perkin Trans. 1*, 58 (1972).
(16) C. W. Shoppee and B. C. Neuman, *J. Chem. Soc. C*, 2767 (1969).
(17) H. Budzikiewicz, J. Buckler, and G. Quinkert, *Monatsh. Chem.*, **98**, 1115 (1967); R. Jones and B. Gallagher, *J. Am. Chem. Soc.*, **81**, 5242 (1959).
(18) E. Dunn and P. Robson, *Chromatography*, **17**, 501 (1965); R. Breslow, S. Baldwin, T. Flechtner, P. Kalicky, S. Liu, and W. Washburn, *J. Am. Chem. Soc.*, **95**, 3251 (1973).
(19) M. Barber and R. M. Elliott, 12th Annual Conference on Mass Spectrometry and Allied Topics, Committee E. 14 A.S.T.M., Montreal, Canada, 1964.
(20) J. L. Occolowitz, *J. Am. Chem. Soc.*, **91**, 5202 (1969).
(21) Tökés, Jones, and Djerassi do not discuss the isomerization reaction in ref 2. The extent of isomerization of d to b can be assayed from data in Table I of their paper. If d, formed by migration of H-18 to the radical site at C-17, isomerizes to b, the resulting fragment ion will be formed with expulsion of a C-18 hydrogen. Conversely, if ion b is formed directly from ion a, all three C-18 hydrogens should be retained. In fact, the former behavior is observed 6% of the time. Similarly, the extent of isomerization reaction b → d could be assessed from the behavior of



the M − C_5H_{10} peak of the 14α-deuterated compound. An apparent typographical error in Table I makes this analysis hazardous. Analogous data for 5α-cholestane (Table II) suggest that the isomerization reaction contributes 10% or less to the genesis of *m/e* 218.



(22) D. H. Williams, R. G. Cooks, and I. Howe, *J. Am. Chem. Soc.*, **90**, 6759 (1968).
(23) The NMR chemical shifts of the C-18 and C-19 angular methyl groups of the oxime cited in ref 14 were erroneously reversed: P. Crabbé, private communication.
(24) For references to the formation of substituted *D*-seconitriles see B. Matkovics, G. Gondos, and Z. Tegyey, *Magy. Kem. Foly.*, **72**, 303 (1966); L. Dlatta and P. Longwvialle, *Bull. Soc. Chem. Fr.*, 1159 (1973).
(25) C. Tegner, *Acta Chem. Scand.*, **6**, 782 (1952).
(26) This isomeric double bond mixture can more conveniently be separated later in the synthetic scheme. It was shown by NMR to consist of the desired isomer XXXI (55%) and the $\Delta^{12(13)}$ isomer XXV (7%). The exocyclic isomer XXIV accounted for the remaining 38%.
(27) G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Am. Chem. Soc.*, **91**, 4871 (1969).