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Mass Spectrometry in Structural and Stereochemical Problems. CCXIII.[1] The Effect of Ring Size upon the Electron Impact Induced Behavior of Steroidal Ketones[2]

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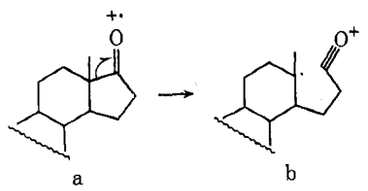
Comparison of the mass spectra of *D*-norpregnan-20-one, pregnan-20-one, and *D*-homopregnan-20-one demonstrates that the relief of ring strain plays a minor role in the determination of the site of charge localization in 20-ketones. The differences observed among the spectra are instead best rationalized on the basis of the stabilities of the ions and neutral species produced by fragmentation. The electron impact induced behavior of *D*-homoandrostan-17a-one and -17-one is qualitatively similar to that of androstan-1-one and -2-one, respectively. The similarity of the mass spectra of *D*-norandrostan-16-one and *D*-norandrostane-16β-carboxylic acid (and several other D-nor steroids) below *m/e* 218, in conjunction with metastable ion evidence, suggests that these low mass ions may arise from a common precursor, the *m/e* 218 ion. The mass spectra of *D*-bishomoandrostan-17b-one and -17a-one are also discussed.

It has long been realized that fragmentations about ring D are of particular diagnostic importance in the interpretation of the electron impact induced behavior of steroids.[5] In order to understand the mechanistic details of these much studied fragmentations, a program was launched in these laboratories to determine the mass spectra of steroids structurally modified in the D ring. Specifically, *D*-nor-, *D*-homo-, and *D*-bishomoandrostanones and -pregnan-20-ones were prepared and their mass spectra were observed.

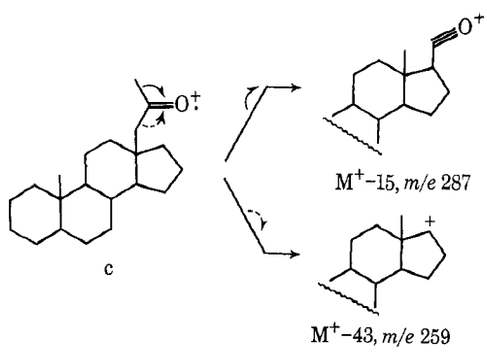
Results and Discussion

Pregnan-20-ones.—The electron impact induced behavior of steroidal ketones has been the subject of numerous investigations.[6] An interesting generalization apparent from these studies is that ions structurally analogous to a usually do not participate directly in the most prevalent fragmentation processes of the molecule. When the carbonyl moiety is contained within a ring, this observation is not surprising. A simple α-cleavage reaction (eq 1), well-known in the mass spectra of aliphatic ketones, generates a species b from which most of the molecule's fragmentations can be rationalized.



(1)

On the other hand, if a molecule such as pregnan-20-one (I) undergoes α cleavage, a fragment ion must be produced (eq 2). Nevertheless, the major fragmentations in the mass spectrum of pregnan-20-one (Figure 2) can best be rationalized on the basis of a molecular ion of structure d.[7] Generation of ion d is clearly a favorable process; cleavage of the C-13–C-17 bond generates a tertiary carbonium ion and a resonance-stabilized radical. In addition, it relieves the strain inherent in the trans-fused hydrindan system



(2)

(1) For paper CCXII, see M. Katoh, D. N. Jaeger, and C. Djerassi, *J. Amer. Chem. Soc.*, submitted for publication.

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(3) Recipient of an IREX fellowship while on leave (1970–1971) from the Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia.

(4) National Institutes of Health Predoctoral Fellow, 1968–1971.

(5) P. de Mayo and R. I. Reed, *Chem. Ind. (London)*, 1481 (1956).

(6) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, Holden-Day, San Francisco, Calif., 1964, Chapter 20.

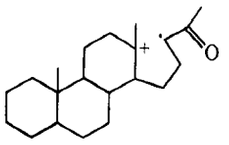
(7) L. Tökes, R. T. LaLonde, and C. Djerassi, *J. Org. Chem.*, **32**, 1020 (1967).

TABLE I

SHIFTS[a] OF MASS SPECTRAL PEAKS OF *D*-HOMOPREGNAN-20-one (II)

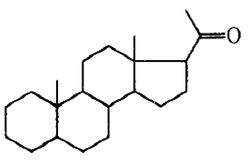
D-Homopregnan-20-one (II)	Isotopic purity	M^+	$M^+ - CH_3$	$M^+ - H_2O$	$M^+ - CH_3 - H_2O$	$M^+ - C_3H_6O$	$M^+ - C_6H_{11}O$
d_0		316	301	298	283	258	217
17a,21,21,21-d_4	92% d_4	320	305	302	287	258	217

[a] Reported shifts are corrected for isotopic impurities as well as ^{13}C contributions and are greater than 90% unless otherwise indicated.

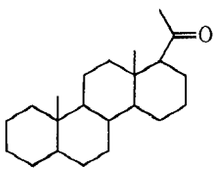


d

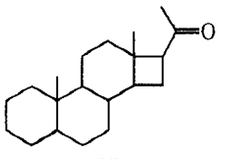
of ring D. It is of considerable interest to evaluate the importance of the latter effect, since it has been invoked as a partial explanation for the preferential fragmentation of pregnane itself about ring D.[8] Thus, *D*-homopregnan-20-one (II), containing a strain-free



I



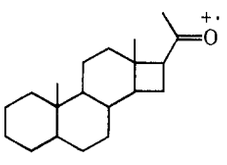
II



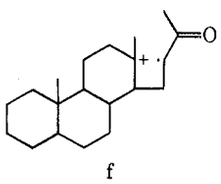
III

trans-decalin system, was prepared. Its mass spectrum (Figure 3) exhibits no evidence for more extensive participation of ions of structure c in the fragmentation processes. The intensity of the M − 43 peak (*m/e* 273) is not enhanced relative to its intensity in the mass spectrum of pregnan-20-one itself. Similarly, deuterium-labeling experiments (Table I) demonstrate that the C-21 methyl group is not implicated in the genesis of the M − 15 peak, exactly as in pregnan-20-one itself.[7] Since the major peaks in both spectra are best rationalized on the basis of molecular ions analogous to d, and not c, it must be concluded that the ring strain inherent in the trans-fused hydrindan system is not an important factor in inducing charge localization in the 13–17 bond.

It is interesting to note that the mass spectrum of *D*-norpregnan-20-one (III, Figure 1) exhibits no peaks which can be attributed to charge localization on the carbonyl group (e). The complete absence of an M − 43 peak (*m/e* 245) in Figure 1 suggests that the highly strained cyclobutane ring of III causes virtually complete charge localization in the 13–16 bond (f) prior to decomposition.



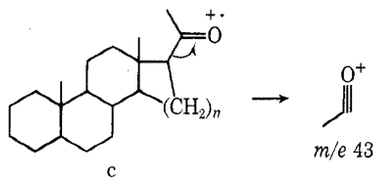
e



f

(8) L. Tökes, G. Jones, and C. Djerassi, *J. Amer. Chem. Soc.*, **90**, 5465 (1968).

A peak appears at *m/e* 43 in the spectra of all three pregnan-20-ones (Figures 1, 2, and 3). Although the *m/e* 43 peak might *a priori* be envisaged as arising directly from a molecular ion of structure c (eq 3), the

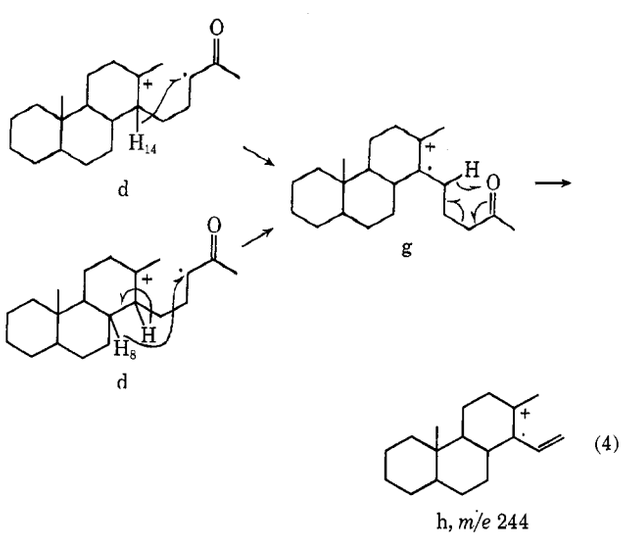


c *m/e* 43 (3)

absence of the peak in the low-voltage spectra of these compounds suggests that it arises from one or more fragment ions. Consequently, variations in the intensity of the *m/e* 43 peak are not readily explicable on the basis of preferential charge localization in the molecular ion.

Although all three 20-ketones appear to fragment predominantly from ions of similar structure, a cursory inspection of Figures 1, 2, and 3 indicates that the fragmentation pattern of *D*-norandrostan-20-one (III) differs dramatically from that of the five- and six-membered ring D compounds. Consideration of these differences sheds considerable light on the mechanisms of fragmentation of pregnan-20-one itself.

M − 58 Peak.—The M − 58 peak appears at *m/e* 244 in the mass spectrum (Figure 2) of pregnan-20-one. It has been proposed[7] that this peak arises largely (60%) by the pathway depicted in eq 4. Abstraction of the C-14 hydrogen atom generates an ion of structure g which can then undergo a McLafferty-type rearrangement to yield the peak at *m/e* 244. It is important to note that the ion g is formed in eq 4 by



d g d h, *m/e* 244 (4)

hydrogen abstraction through a transition state involving a five-membered ring. A significant portion (40%) of the mass 244 ion is formed by the abstraction of the unactivated hydrogen atom at C-8 (eq 4).

TABLE II

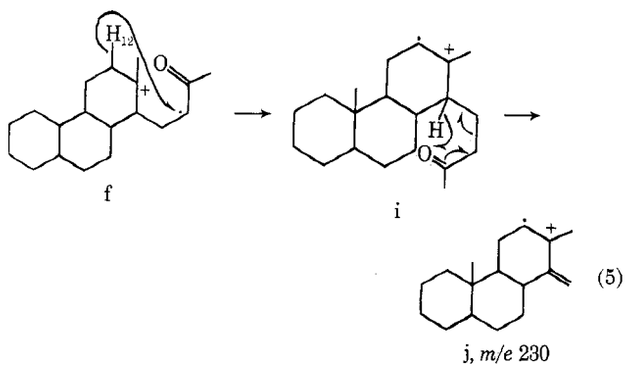
SHIFTS[a] OF MASS SPECTRAL PEAKS OF *D*-NORPREGNAN-20-ONE (III)

D-Norpregnan-20-one (III)	Isotopic purity	M+	M+ − CH_3	M+ − H_2O	M+ − CH_3 − H_2O	M+ − C_3H_6O	M+ − C_4H_6O	M+ − C_4H_7O	M+ − C_4H_9O	M+ − C_5H_9O
d_0		288	273	270	255	230	218	217	215	203
16,21,21,21-d_4	95% d_4	292	277	274	259	230	218	217	215	203

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

The prevalence of the latter process must be attributed to the well-known preference for hydrogen abstraction through a six-membered ring.

The very abundant ion of mass 230 in the spectrum of *D*-norpregnan-20-one (Figure 1) presumably arises through a similar mechanism, although this has not been fully substantiated by deuterium labeling experiments (Table II). Abstraction of a C-12 hydrogen through a six-membered transition state would generate the ionized keto olefin i, which can undergo a McLafferty rearrangement to an ion of mass 230 (eq 5).

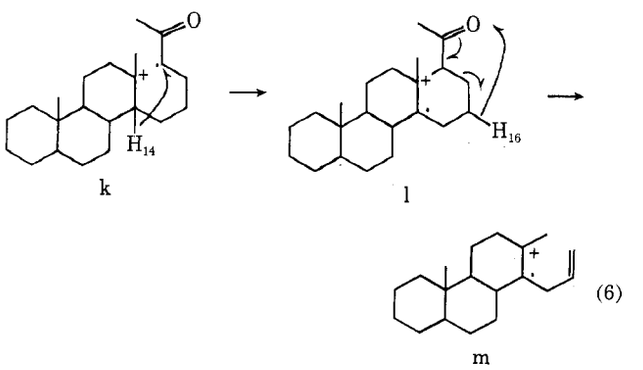


f i (5)

j, *m/e* 230

The dramatic increase in the abundance of the M − 58 ion in the spectrum of *D*-norpregnan-20-one (III) must be attributed to the presence of activated hydrogens at C-12 which can be extracted through the very favorable six-membered transition state.

Abstraction of an activated hydrogen atom from C-14 in the molecular ion k of *D*-homopregnan-20-one (II) also involves a six-membered ring transition state. The small size of the M − 58 peak (*m/e* 254) in Figure 3 must therefore be attributed to the unactivated nature of the C-16 hydrogen which needs to participate in the McLafferty rearrangement (eq 6).



k l (6)

m

M − 70 Peak.—This fragmentation gives rise to the intense peak at *m/e* 218 in the mass spectrum of *D*-norpregnan-20-one (III) (Figure 1) and the weak peak

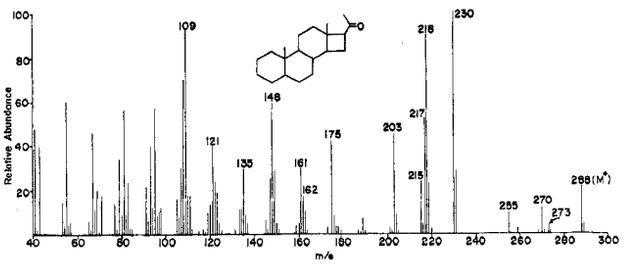


Figure 1.—Mass spectrum of *D*-nor-5α-pregnan-20-one.

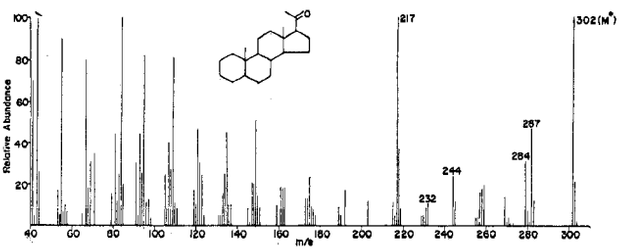


Figure 2.—Mass spectrum of 5α-pregnan-20-one.

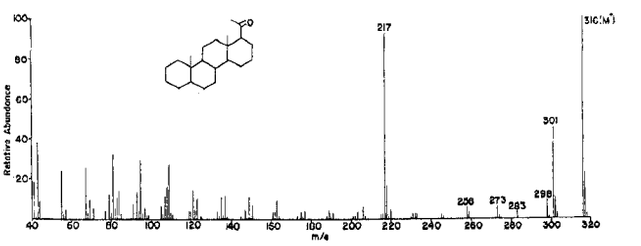
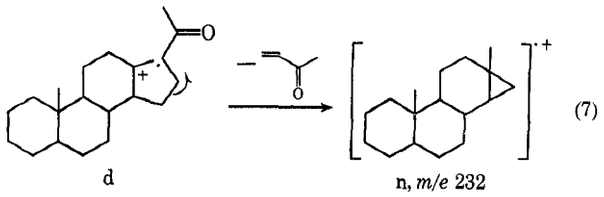


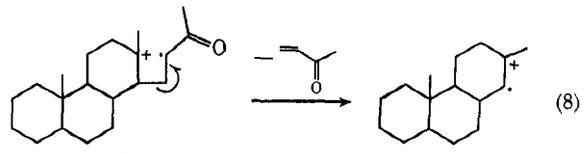
Figure 3.—Mass spectrum of *D*-homo-5α-pregnan-20-one.

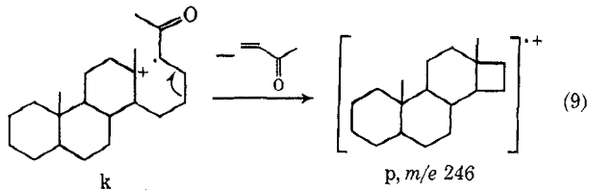
at *m/e* 232 in the mass spectrum of pregnan-20-one (1) (Figure 2); the corresponding peak is not observed in the mass spectrum of *D*-homopregnan-20-one (II) (Figure 3).

Deuterium-labeling experiments on pregnan-20-one demonstrated[7] that this process involves the expulsion of C-16, C-17, C-20, and C-21, as depicted in eq 7. The increased intensity of the corresponding peak in the spectrum of *D*-norpregnan-20-one (Figure 1) must be attributed to the greater stability of an ionized double bond (o) as compared to an ionized cylopropane (n). Similarly, the complete absence of the M − 70 peak in the spectrum of *D*-homopregnan-20-one must be attributed to the even less favored character of the ionized cyclobutyl species p.

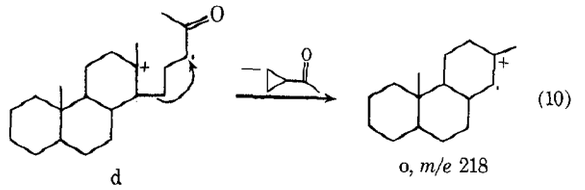
The variation in the abundance of the M − 70 peak can thus be rationalized on the basis of the stability of the resulting ionic species. Conversely, the variation in the abundance of the *m/e* 218 peak in the spectra of the three ketones is attributable to the stability of the neutral species produced. The expulsion of an olefin

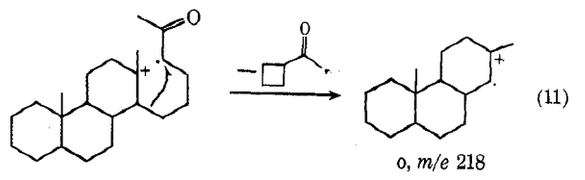

d n, m/e 232 (7)


f o, m/e 218 (8)

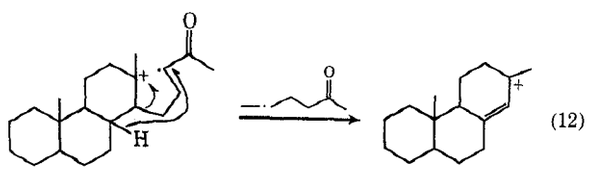

k p, m/e 246 (9)

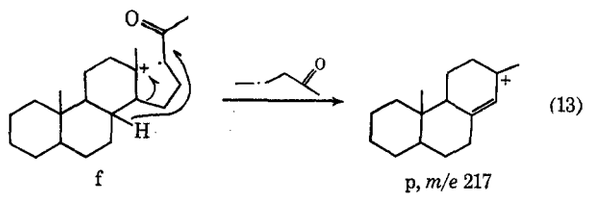
(eq 8) is energetically preferable to the expulsion of a cyclopropane (eq 10) or cyclobutane (eq 11).

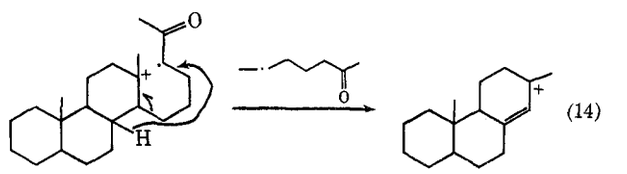

d o, m/e 218 (10)


o, m/e 218 (11)

m/e **217 Peak.**—All three ketones exhibit an intense peak at *m/e* 217, corresponding to the elimination of ring D with an additional hydrogen atom. Deuterium-labeling experiments have implicated C-8 and C-14

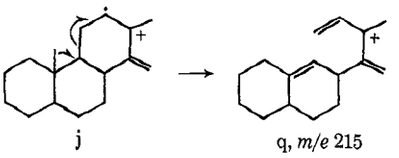

d p, m/e 217 (12)


f p, m/e 217 (13)


k p, m/e 217 (14)

as the sources of the extra hydrogen atom in the fragmentation of pregnan-20-one itself (eq 12).[7] Deuterium-labeling experiments have not been performed on *D*-nor- or *D*-homopregnan-20-one to establish the origin of the extra hydrogen atom; it appears plausible, however that the *m/e* 217 peak in Figures 1 and 3 arises in an analogous manner (eq 13 and 14).

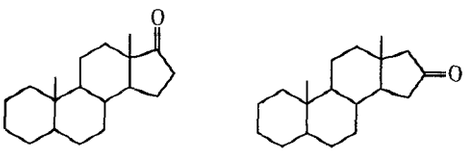
m/e **215 Peak.**—Metastable ion evidence suggests that the *m/e* 215 peak in the mass spectrum of *D*-norpregnan-20-one (Figure 1) is formed by the elimination of a methyl group from the *m/e* 230 peak (eq 15).


j q, m/e 215 (15)

The ion of mass 215 in the spectrum of pregnan-20-one (Figure 2) probably arises in an identical manner.

Other Fragmentations.—The mass spectrum of *D*-norpregnan-20-one (Figure 1) exhibits a series of peaks at *m/e* 203, 175, 162, 161, 148, and 109 which are characteristic of all the D-nor steroids prepared in this study. Discussion of the genesis of these ions will be deferred to the subsequent section dealing with *D*-norandrostan-16-one and *D*-norandrostane-16β-carboxylic acid, since more extensive deuterium-labeling data are available for the latter compound.

Androstan-16-, -17-, -17a-, and -17b-ones.—The electron impact induced behavior of androstan-16-one (IV)[9] and androstan-17-one (V)[10] has been the object of careful study, and a number of unusual mechanistic proposals have been advanced to account for the fragmentations of these compounds.


V IV

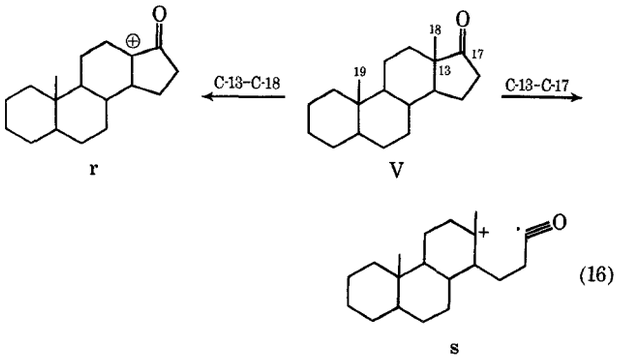
It was of interest, therefore, to compare the mass spectra of analogous *D*-nor, *D*-homo, and *D*-bishomo ketones; the effect of adding or removing a methylene group adjacent to the carbonyl moiety should shed considerable light on the mechanisms of a number of very favorable process in the mass spectra of steroidal ketones.

M − 15 Peak.—The M − 15 peak appears in the spectra of all the keto steroids investigated in this study. Deuterium-labeling experiments performed on androstan-17-one (V) indicated that the C-19 methyl group was eliminated three times as readily as the C-18 methyl group.[10] This observation was attributed to preferential charge localization in the C-13–C-17 bond, rather than the required C-13–C-18 bond (eq 16).

It was relevant, therefore, to determine the origin of the M − 15 peak in the *D*-homo steroids. In *D*-homoandrostan-17a-one (VI), the ratio of C-19 loss to C-18 loss decreases to 1:1 (*cf.* Table III). This observation

(9) C. Beard, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 269 (1964).

(10) L. Tökes, R. T. LaLonde, and C. Djerassi, *J. Org. Chem.*, **32**, 1012 (1967); G. Jones and C. Djerassi, *Steroids*, **10**, 653 (1967).

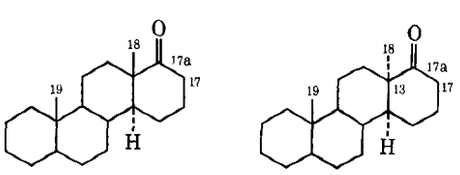


r V s (16)

TABLE III
EFFECT OF STRUCTURE ON THE RATIO OF C-19 METHYL LOSS TO C-18 METHYL LOSS IN STEROIDAL KETONES

Compd	C-19/C-18
Androstan-17-one (V)	3:1
Androstan-2-one (IX)	1:1
D-Homoandrostan-17a-one (VI)	1:1
D-Homo-13α-androstan-17a-one (VII)	3:1

is, in itself, consistent with the earlier explanation, because the *trans*-decalone system of the *D*-homo steroid should be less strained than the *trans*-hydrindanone system of the normal steroid; cleavage of the 13–17a bond should, therefore, be less favorable. However, the *cis*-decalone system of *D*-homo-13α-androstan-17a-one (VII) is more strained than the *trans*-decalone system. Nevertheless, the ratio of C-19 loss to C-18 loss increases to 3:1, despite the apparent driving force favoring cleavage of the 13–17a bond.

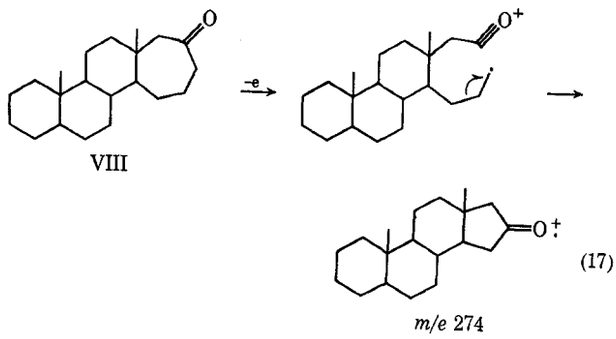


VI VII

These results suggest that the original explanation[10] for the ratio observed in the spectra of androstan-17-one is oversimplified. Until more extensive comparisons are available, the factors determining the ratio of methyl elimination must remain poorly understood.

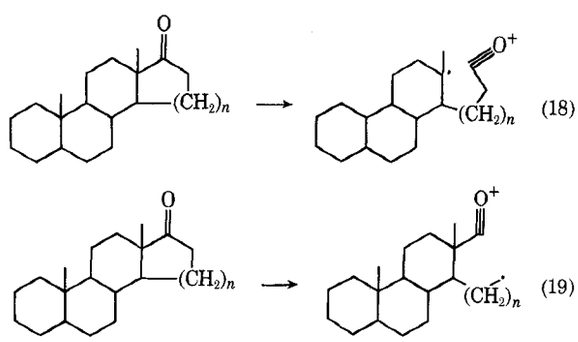
M − H_2O Peak.—Extensive deuterium-labeling experiments (Table V) on *D*-homoandrostan-17a-one (VI) demonstrate that the elimination of water is a random process, with no labeled position accounting for more than a small fraction of the hydrogen atoms eliminated. A similar conclusion must be drawn from the *D*-homo 17 ketones (Table VI) and *D*-bishomo (Tables VII and VIII) steroids, although on the basis of much less extensive labeling data. This is in complete accord with the results already described for the elimination of water from androstan-17-one.[10]

M − C_2H_4 Peak.—The second most intense peak in the mass spectrum of *D*-bishomoandrostan-17a-one (VIII, Figure 8) appears at *m/e* 274, corresponding to the elimination of 28 mass units from the molecular ion. Deuterium-labeling experiments suggest that the process occurs as depicted in eq 17. It is interesting to note that the elimination of ethylene is not observed in the spectra of any of the other ketones investigated



VIII *m/e* 274 (17)

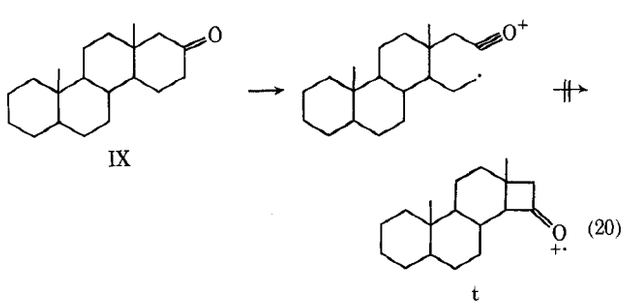
in this study. This observation can be rationalized, however. In those ketones in which the carbonyl group is adjacent to the angular methyl [*D*-norandrostan-16-one (XI), *D*-homoandrostan-17a-one (VI), and *D*-bishomoandrostan-17b-one (XV)], charge localization occurs predominantly between the carbonyl group and the tertiary carbon (eq 18), not the carbonyl group and the primary carbon (eq 19), as required by the mechanism depicted in eq 17.



(18)

(19)

The absence of an M − 28 peak in the spectrum of *D*-homoandrostan-17-one (IX, Figure 6) cannot be attributed to this effect. The explanation must lie in the greater strain inherent in the cyclobutane system t, which would form after the elimination of ethylene (eq 20).



IX t (20)

m/e **230 and 231.**—The most intense peaks in the mass spectrum of *D*-homoandrostan-17-one (IX, Figure 7) appear at *m/e* 230 and 231. Although the absence of extensive deuterium labeling data makes detailed discussion of the origin of these peaks difficult, the observation of analogous peaks in the mass spectrum of androstan-2-one (X)[11] permits a qualitative discussion of their genesis.

The *m/e* 231 peak in the mass spectrum[11] of androstan-2-one (X) arises by the elimination of a C_3H_7 frag-

(11) J. E. Gurst and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 5542 (1964).

TABLE IV

SHIFTS[a] OF MASS SPECTRAL PEAKS OF *D*-NORANDROSTANE-16β-CARBOXYLIC ACID (XVI)

D-Norandrostan-16β-carboxylic acid (XVI)	Isotopic purity	M+	M+ − CH_3	M+ − $C_2H_4O_2$	M+ − $C_3H_4O_2$	M+ − $C_5H_5O_2$	M+ − $C_4H_7O_2$	M+ − $C_6H_{11}O_2$	M+ − $C_8H_{13}O_2$	M+ − $C_8H_{14}O_2$	M+ − $C_{11}H_{17}O_2$
d_0	...	290	275	230	218	217	203	175	149	148	109
3-d_1	85% d_1	291	276	231	219	218	204	176	150 (90%)	149 (80%)	110 (70%)
									149 (10%)	148 (20%)	109 (30%)
14α-d_1	80% d_1	291	276	231 (60%)	219 (80%)	218 (80%)	204 (80%)	176 (60%)	150 (5%)	149 (20%)	110 (<20%)
				230 (40%)	218 (20%)	217 (20%)	203 (20%)	175 (40%)	149 (95%)	148 (80%)	109 (>80%)
15α-d_1	58% d_1	291	276	231 (85%)	218	217	203	176 (40%)	149	149 (10%)	110 (20%)
				230 (15%)				175 (60%)		148 (90%)	109 (80%)
16α-d_1	98% d_1	291	276	230	218	217	203	175	149	148	110 (20%)
											109 (80%)

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

TABLE V

SHIFTS[a] OF MASS SPECTRAL PEAKS OF *D*-HOMOANDROSTAN-17a-one (VI)

D-Homoandrostan-17a-one (VI)	Isotopic purity	M+	M+ − CH_3	M+ − H_2O	M+ − CO	M+ − H_2O − CH_3	M+ − CO − CH_3	M+ − C_4H_9	M+ − C_4H_{10}	M+ − C_4H_7O	M+ − C_4H_9O	M+ − $C_5H_{13}O$	M+ − $C_9H_{17}O$
d_0		288	273	270	260	255	245	231	230	217	215	189	149
3-d_1	98% d_1	289	274	271	261	256	246	232	231	218	216	190	150
14α-d_1	90% d_1	289	274	271 (80%)	261	256	246	232	231	218 (50%)	215	189	149
				270 (20%)						217 (50%)			
16,16-d_2	98% d_2	290	275	272	262	257	247	233	231 (50%)	217	215	189	149
									323 (50%)				
17,17-d_2	93% d_2	290	275	272	262	257	247	233	232	217	215	189	149
18,18,18-d_3	98% d_2	291	276 (50%)	273	263	258	248	234	230	220	218	192 (50%)	149
			273 (50%)									189 (50%)	

[a] Reported shifts are corrected for isotopic impurities as well as ^{13}C contributions and are greater than 90% unless otherwise indicated.

TABLE VI

SHIFTS[a] OF MASS SPECTRAL PEAKS OF *D*-HOMOANDROSTAN-17-ONE (VIII)

D-Homoandrostan-17-one (VIII)	Isotopic purity	M+	M+ − CH_3	M+ − H_2O	M+ − CH_3 − H_2O	M+ − C_4H_9	M+ − C_5H_9O
d_0		288	273	270	255	231	230
d_4	75% d_4	292	277	274	259	235	230

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

TABLE VII

SHIFTS[a] OF MASS SPECTRAL PEAKS OF *D*-BISHOMOANDROSTAN-17a-ONE (VIII)

D-Bishomoandrostan-17-one (VIII)	Isotopic purity	M+	M+ − CH_3	M+ − H_2O	M+ − C_2H_4	M+ − CH_3 − H_2O	M+ − C_5H_8O	M+ − C_5H_9O
d_0		302	287	284	274	269	244	217
17,17,17b,17b-d_4	80% d_4	306	291	288	276	273	244	217

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

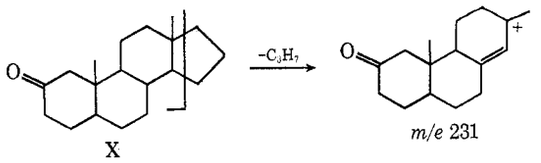
TABLE VIII

SHIFTS[a] OF MASS SPECTRAL PEAKS OF *D*-BISHOMOANDROSTAN-17b-ONE (XV)

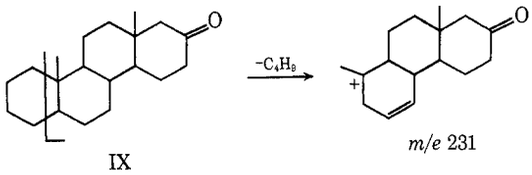
D-Bishomoandrostan-17b-one (XV)	Isotopic purity	M+	M+ − CH_3	M+ − H_2O	M+ − C_5H_7	M+ − C_5H_9O
d_0		302	287	284	259	217
17a,17a-d_2	98% d_2	304	289	286	261	217

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

ment from ring D (eq 21). High-resolution mass spectrometry on the *m/e* 231 peak of *D*-homoandrostan-17-one (IX) indicates that it arises by the elimination of C_4H_9, and deuterium labeling experiments (Table VI) demonstrate that ring D hydrogens are retained. It appears plausible that fragmentation is occurring about ring A as depicted in eq 22.



X *m/e* 231 (21)



IX *m/e* 231 (22)

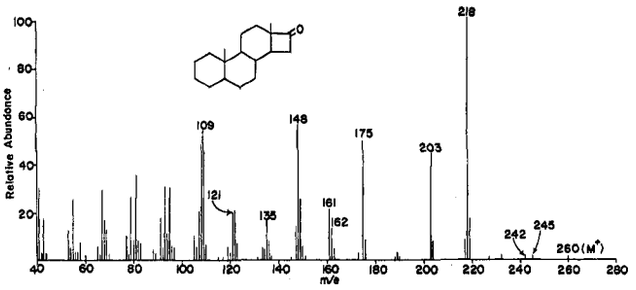
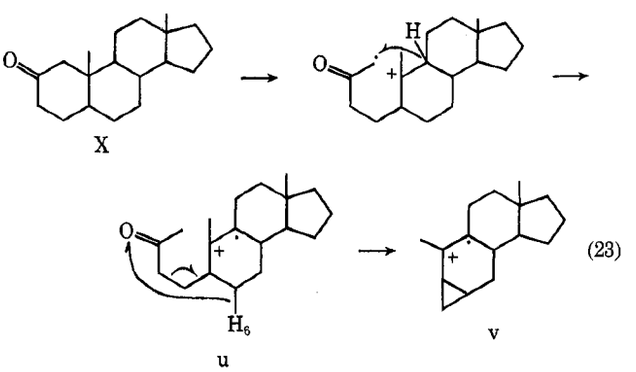
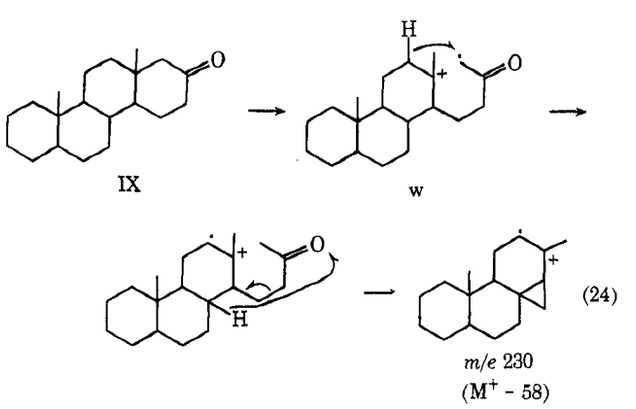


Figure 4.—Mass spectrum of *D*-nor-5α-androstan-16-one.

The genesis of the *m/e* 216 peak in the mass spectrum of androstan-2-one has been fully elucidated[11] by deuterium labeling; the proposed mechanism is depicted in eq 23. Transfer of a hydrogen atom to C-1 generates the ionized keto olefin u, which undergoes fragmentation by abstracting a C-6 hydrogen atom (u → v).



High-resolution mass spectrometry on the *m/e* 230 peak in the spectrum of *D*-homoandrostan-17-one (IX) is in complete accord with the occurrence of an analogous process in the formation of this ion (eq 24). Moreover, deuterium-labeling experiments demonstrate that C-16 and C-17a are eliminated in this fragmentation.



The *m/e* 230 peak in the mass spectrum of androstan-17-one (Figure 5) arises in a mechanistically distinct manner; its genesis has been discussed in an earlier publication.[10]

Deuterium-labeling experiments (Table V) indicate that the small peaks at *m/e* 230 and 231 in the spectrum of *D*-homoandrostan-17a-one (Figure 6) are formed by several distinct mechanistic pathways, and that the plausible cleavage depicted in eq 25 is not the predominant source of the *m/e* 231 ion. It is interesting to note then, that cleavage about ring A is observed in the spectrum of *D*-homoandrostan-17-one (IX) but not in the spectrum (Figure 6) of *D*-homoandrostan-17a-one (VI). This difference can be attributed to the greater stability of ions of structure x *vs.* those of structure w. Apparently, charge localization in the 1–10 bond (y) can compete with the formation of the species w.

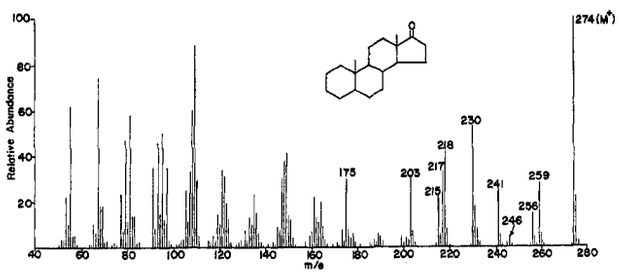
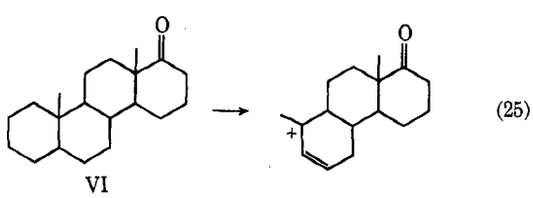
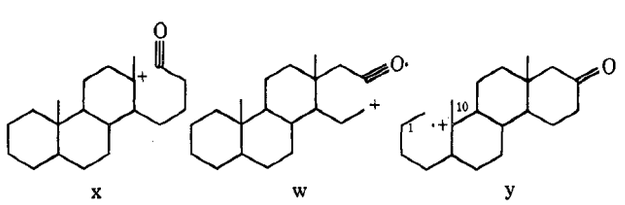


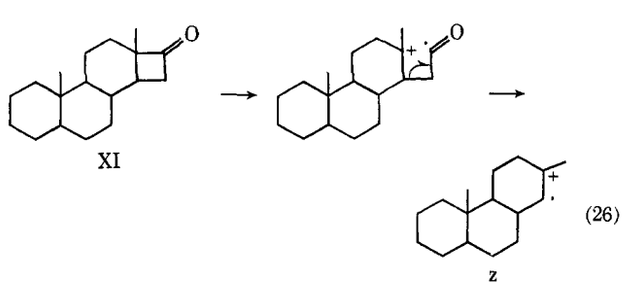
Figure 5.—Mass spectrum of 5α-androstan-17-one.

Figure 6.—Mass spectrum of *D*-homo-5α-androstan-17a-one.





m/e **218 Peak.**—The most abundant peak in the spectrum (Figure 4) of *D*-norandrostan-16-one (XI) appears at *m/e* 218. This process corresponds to the elimination of ring D as ketene, without hydrogen transfer (eq 26). Charge localization in the 13–16



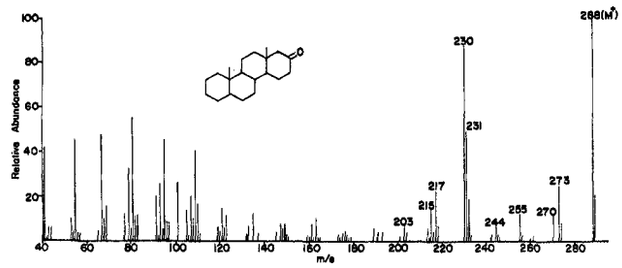


Figure 7.—Mass spectrum of *D*-homo-5α-androstan-17-one.

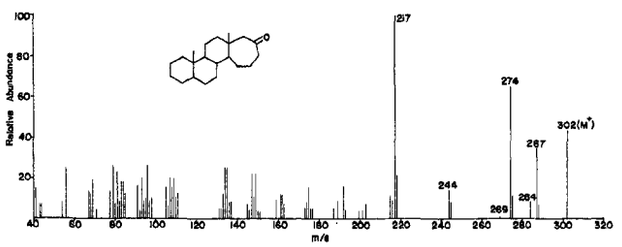
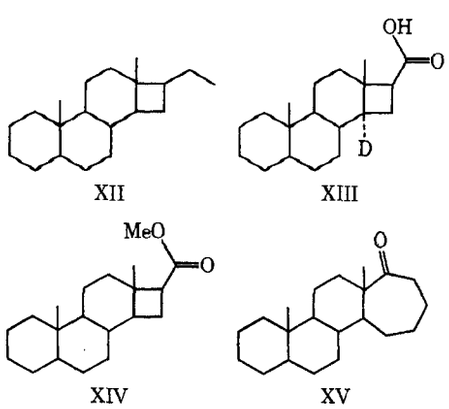


Figure 8.—Mass spectrum of *D*-bishomo-5α-androstan-17a-one.

bond generates a tertiary carbonium ion and a stabilized radical, in addition to relieving the strain inherent in the trans-fused cyclobutanone system. The elimination of ketene generates the ionized olefin z.

Although deuterium-labeling experiments on *D*-norpregnane (XII)[12] and *D*-norpregnan-20-one (III) demonstrate that a reciprocal hydrogen transfer is not involved in the genesis of the mass 218 ion, different results are obtained for *D*-norandrostane-16β-carboxylic acid-*14α-d*$_1$ (XIII); approximately 20% of the 14-deuterium is eliminated, and labels at C-15 and C-16 are completely lost (Table IV). It appears likely, then, that the back transfer of hydrogen involves the acidic hydrogen on the carboxyl oxygen. The observation that the elimination of the 14-deuterium decreases to less than 5% in the genesis of the ion of mass 218 of the corresponding methyl ester XIV is consistent with this conclusion. Further experimentation would be necessary to clarify the complete mechanism of this unusual process.



XII XIII XIV XV

The mass spectrum of androstan-17-one (Figure 5) also exhibits a peak at *m/e* 218. Deuterium-labeling experiments[10] were consistent with the mechanism depicted in eq 27. The virtual absence of a peak at *m/e*

(12) G. Eadon, S. Popov, and C. Djerassi, submitted for publication.

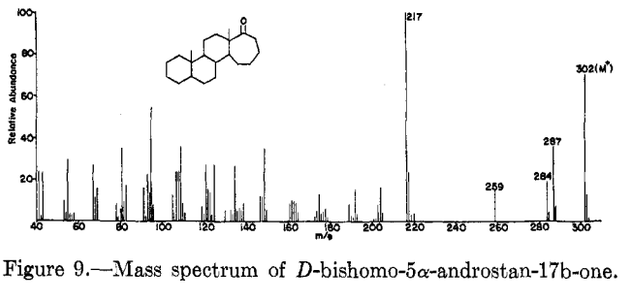
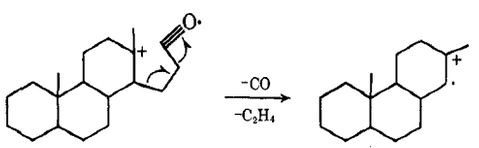


Figure 9.—Mass spectrum of *D*-bishomo-5α-androstan-17b-one.

218 in the spectra (Figures 6 and 9) of *D*-homoandrostan-17a-one (VIII) and *D*-bishomoandrostan-17b-one

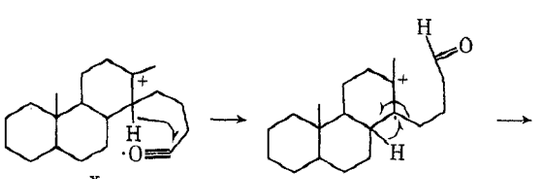


s o, *m/e* 218 (27)

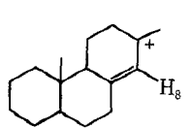
(XV) is in complete harmony with this mechanism. Formation of a mass 218 ion by these compounds would require the elimination of cyclopropane and cyclobutane, respectively.

m/e **217 Peak.**—The *m/e* 217 peak in the mass spectrum (Figure 5) of androstan-17-one arises by the elimination of ring D and an additional hydrogen atom. Deuterium labeling demonstrated that the extra hydrogen was partially (50%) extracted from C-14; abstraction of the remaining 50% was a random process.[10]

A similar mechanism pertains to *D*-homoandrostan-17a-one (eq 28). The ring D labels were completely eliminated, along with 50% of the C-14 hydrogen.[13]



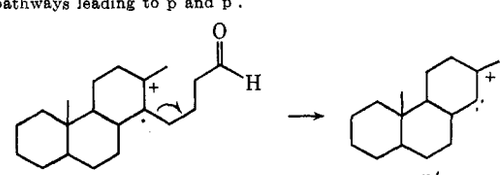
x aa



p (28)

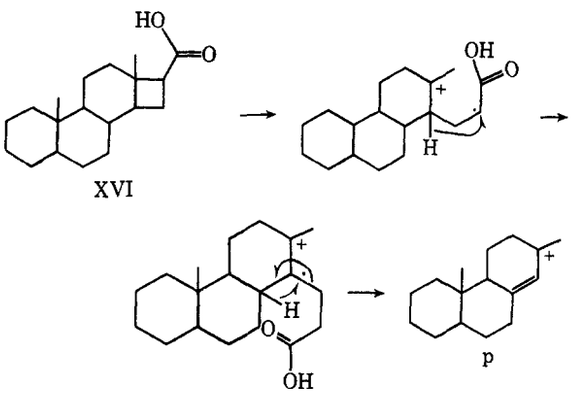
Very abundant peaks appear at *m/e* 217 in the mass spectra of *D*-bishomoandrostan-17a-one (VIII, Figure 8) and *D*-bishomoandrostan-17b-one (XV, Figure 9). Deuterium labeling experiments (Tables VII and VIII) demonstrate that these processes involve the expulsion of ring D, so it appears likely that a similar mechanism prevails.

(13) The 1,2 shift of the C-8 hydrogen (aa → p) is postulated solely to avoid the formation of the presumably high energy ionized carbene p′. Work is currently underway in these laboratories to differentiate between the pathways leading to p and p′.



aa p′

In the mass spectrum (Figure 4) of *D*-norandrostan-16-one (XI) the *m/e* 217 peak is small. The process becomes more favorable in the electron impact induced behavior of the 16β-carboxylic acid (XVI). Deuterium-labeling experiments (Table IV) demonstrate that only 25% of the abstracted hydrogen originates from C-14. The lowered specificity of this process in the D-nor steroids probably can be explained on the basis of the ring sizes involved in the transition states for hydrogen abstraction. Removal of the C-14 hydrogen requires a four-membered ring in the transition state (eq 29), while a competing process, the abstrac-



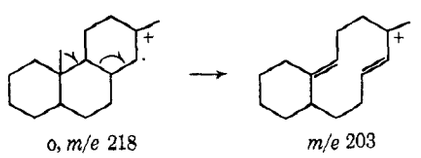
(29)

tion of a C-12 hydrogen, proceeds through a more favorable six-membered transition state.

Other Fragmentations.—The mass spectra of *D*-norpregnane (XII),[12] *D*-norandrostane,[12] *D*-norandrostan-16-one (XI, Figure 4), and *D*-norandrostan-16β-carboxylic acid (XV, Figure 10) are virtually identical below *m/e* 218. This similarity, coupled with the uniformly high intensity of the *m/e* 218 peak and the observation that the ring D labels are largely eliminated (Table IV), suggests that the *m/e* 218 peak is the precursor for most of these low mass ions. Metastable evidence is completely consistent with this hypothesis.

The peak at *m/e* 203 in Figures 4 and 10 arises by the elimination of methyl from the *m/e* 218 ion, according to metastable ion evidence. An exactly similar process has been observed[12] in the spectra of the D-nor steroid hydrocarbons, which also generate a mass 218 ion.

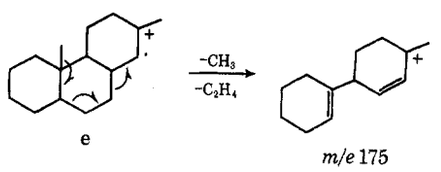
Metastable ion evidence suggests that the ion of mass 175 also arises from the *m/e* 218 ion. In agreement with this observation, the peak remains largely at *m/e* 175 when the acid XV is labeled in ring D, and shifts



o, *m/e* 218 *m/e* 203

(30)

completely when the acid is labeled in ring A (Table IV). A plausible representation of this process appears in eq 31.



e *m/e* 175

(31)

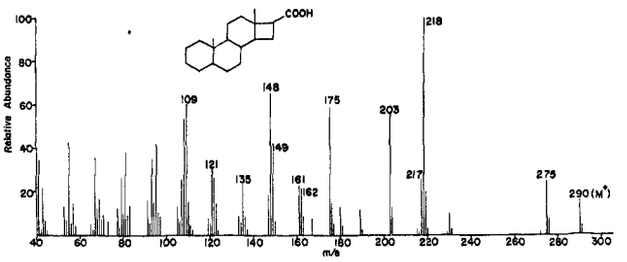
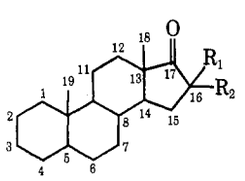


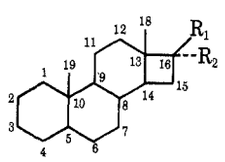
Figure 10.—Mass spectrum of *D*-nor-5α-androstane-16β-carboxylic acid.

The shifts of a number of additional peaks in the spectrum of *D*-norandrostane-16β-carboxylic acid are listed in Table IV. In the absence of more complete deuterium-labeling data, it does not appear worthwhile to speculate on the genesis of these ions.

Synthesis.—The D-nor ketones utilized in this investigation were prepared essentially according to the procedure of Meinwald, *et al.*[14] Androstan-17-one (V) was converted to 16-oximinoandrostan-17-one (XVI) by treatment with isoamyl nitrite in *tert*-butyl alcohol containing potassium *tert*-butoxide. The oxime was converted to the corresponding diazo ketone (XVII) by reaction with chloramine. Irradiation of the diazo ketone yielded *D*-norandrostane-16β-carboxylic acid (XV). Reaction of the acid with methyllithium yielded *D*-norpregnan-20-one (III). Baeyer–Villager oxidation of III gave, after hydrolysis of the intermediate acetate, *D*-norandrostan-16β-ol (XVIII). Jones oxidation gave *D*-norandrostan-16-one (XI).



V, $R_1 = R_2 = H$
XVI, R = NOH
XVI, $R_1 = H$; $R_2 = N_2$



XV, $R_1 = CO_2H$; $R_2 = H$
III, $R_1 = O{=}C{-}CH_3$; $R_2 = H$
XVIII, $R_1 = OH$; $R_2 = H$
XI, $R_1 = R_2 = O$

The preparation of several deuterated derivatives of *D*-norpregnan-20-one and *D*-norandrostane-16β-carboxylic acid was straightforward. Base-catalyzed exchange of the ketone III in deuteriomethanol gave *D*-norpregnan-20-one-*16,21,21,21-d*$_4$. *D*-norandrostane-16β-carboxylic acid-*3-d*$_1$ was prepared by ring contraction of androstan-17-one-*3-d*$_1$[10] in the usual manner.

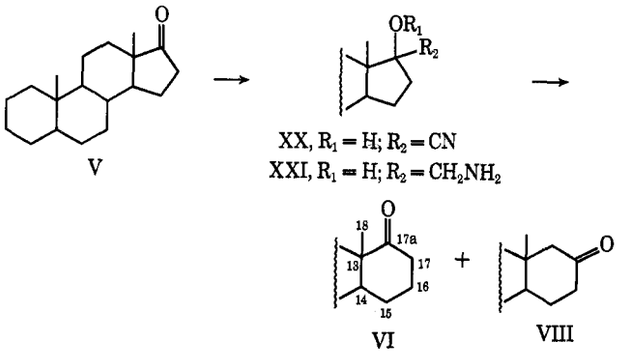
The synthesis of *D*-norandrostane-16β-carboxylic acid-*14α-d*$_1$ and -*15α-d*$_1$ required Δ^{14}-androstan-17-one (XIX), whose preparation has already been described.[12] Deuterioboration of the unsaturated ketone XIX, followed by hydrolytic cleavage of the alkylborane intermediate and Jones oxidation gave androstan-17-one-*14α-d*$_1$; conversion to *D*-norandrostane-16β-carboxylic acid-*14α-d*$_1$ was accomplished routinely. Alternatively, hydroboration of Δ^{14}-androsten-17-one (XIV), followed by hydrolytic cleavage with propionic acid-*O-d* and Jones oxidation gave an-

(14) J. Meinwald, L. Labana, and T. Wheeler, *J. Amer. Chem. Soc.*, **92**, 1006 (1970); see also M. P. Cava and E. Moroz, *ibid.*, **84**, 115 (1962); J. L. Mateos and C. Chao, *Bol. Inst. Quim. Univ. Nac. Auton. Mex.*, **13**, 3 (1961); G. Muller, C. Huynh, and J. Mathieu, *Bull. Soc. Chim. Fr.*, 296 (1962).

drostan-17-one-*15α-d*$_1$ which was converted into *D*-norandrostane-16β-carboxylic acid-*15α-d*$_1$.

The preparation of *D*-homoandrostan-17a-one (VI) and *D*-homoandrostan-17-one (VIII) was accomplished using well-known reactions (Scheme I).[15]

SCHEME I

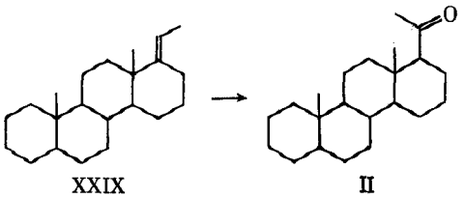


Condensation of androstan-17-one (V) with hydrogen cyanide gave the cyanohydrin XX. Catalytic reduction yielded the hydroxy amine XXI, which after treatment with dilute aqueous nitrous acid gave *D*-homoandrostan-17- and -17a-one.

The preparation of several labeled derivatives of these ketones was straightforward. Exchange of the parent ketones in deuteriomethanol containing catalytic amount of sodium deuteroxide gave *D*-homoandrostan-17a-one-*17,17-d*$_2$ and *D*-homoandrostan-17-one-*16,16,17*a,*17*a-*d*$_4$. Homologation of androstan-17-one-*3-d*$_1$[10] and androstan-17-one-*14*a-*d*$_1$[12] gave *D*-homoandrostan-17a-one-*3-d*$_1$ and -*14*a-*d*$_1$. Androstan-*17*-one-*16,16-d*$_2$ was prepared by base-catalyzed exchange of androstan-17-one. Homologation gave *D*-homoandrostan-17a-one-*16,16-d*$_2$.

The preparation of *D*-homandrostan-17a-one-*18,18,-18-d*$_3$ (XXVIII) was accomplished by total synthesis as depicted in Scheme II.[16,17]

Reaction of *D*-homopregn-Δ^{17,20}-ene (XXIX)[12] with diborane yielded an organoborane which was converted directly[18] into *D*-homopregnan-20-one (II).



D-Bishomoandrostan-17a-one (VIII) was prepared by the homologation of *D*-homoandrostan-17a-one (VI). Condensation of the ketone VI with hydrogen cyanide gave the cyanohydrin XXX; catalytic hydrogenation gave the hydroxy amine XXXI, which

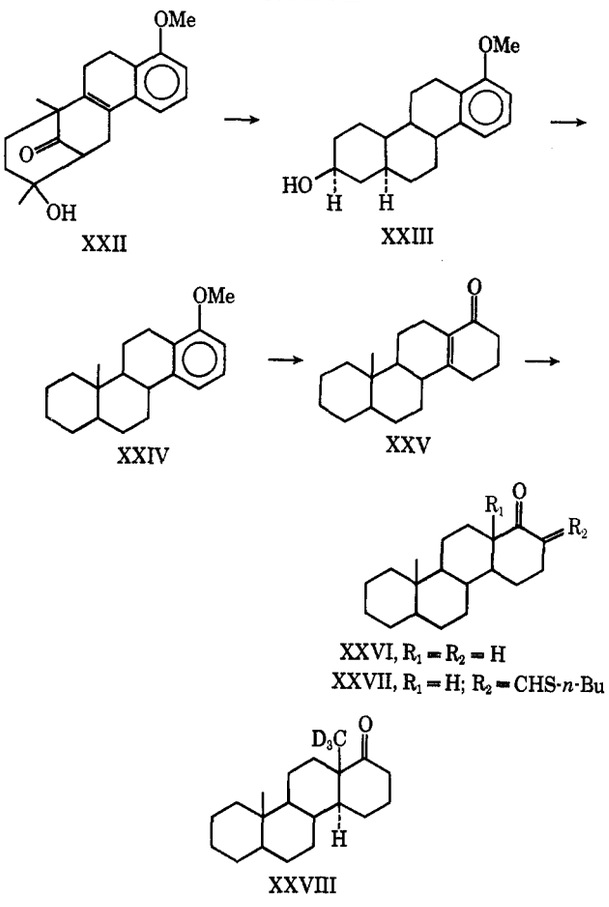
(15) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 583.

(16) W. S. Johnson, J. Szmuskovicz, E. R. Rogier, H. I. Hadler, and H. Wynberg, *J. Amer. Chem. Soc.*, **78**, 6285 (1956); W. S. Johnson, B. Bannister, and R. Pappo, *ibid.*, **78**, 6331 (1956).

(17) We gratefully acknowledge a gift of the tetracyclic ketone XXII from Professor W. S. Johnson of this department.

(18) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2951 (1961).

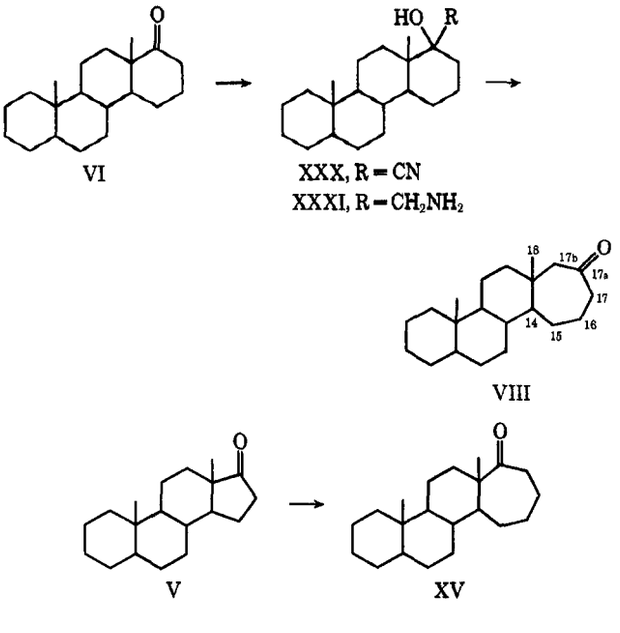
SCHEME II



yielded the desired ketone VIII upon Tiffeneau rearrangement.

D-Bishomoandrostan-17b-one (XV) was prepared by bishomologation of androstan-17-one using diazomethane.

The corresponding α-deuterated *D*-bishomoandrostan-17a- and -17b-ones were prepared by base-catalyzed exchange of the unlabeled ketones.



Experimental Section[19]

D-**Norpregnan-20-one (III) and *D*-Norpregnan-20-one-*16,21,21,21-d*$_4$.**—The preparation of these compounds has already been described.[12]

D-**Norandrostan-16-one (XI).**—*D*-Norandrostan-16β-ol[12] (90 mg) was oxidized by treatment with Jones reagent at room temperature. After 15 min, the solution was taken up into methylene chloride, washed thoroughly with water, dried over $MgSO_4$, and concentrated under vacuum. Preparative tlc [hexane–ether (1:1) eluent] gave *D*-norandrostan-16-one (XI) (52 mg) as an oil.

Anal. Calcd for $C_{18}H_{28}O$: mol wt, 250. Found: M^+, 250.

D-**Norandrostane-16β-carboxylic Acid (XV).**—The preparation of this compound has already been described.[12]

D-**Norandrostane-16β-carboxylic Acid-*3-d*$_1$, -*14*α-*d*$_1$, and -*15-d*$_1$.**—These compounds were prepared from androstan-17-one-*3-d*$_1$,[7] androstan-17-one-*14*α-*d*$_1$, and androstan-17-one-*15-d*$_1$,[12] respectively, by ring contraction according to a procedure which has already been reported.[12]

D-**Norandrostane-16β-carboxylic Acid-*16*α-*d*$_1$.**—The diazo ketone XVII (30 mg)[12] was irradiated in a solution of dry tetrahydrofuran (100 ml) and deuterium oxide (40 ml) containing 120 mg of sodium bicarbonate. The irradiation and isolation were carried out in the usual manner.[12] Pure *D*-norandrostane-16β-carboxylic acid-*16*α-*d*$_1$ (13 mg, mp 204–205°) was isolated after recrystallization from methanol.

D-**Homopregnan-20-one (II).**—An ethereal solution of *D*-homopregn-$\Delta^{17a,20}$-ene (30 mg)[12] was treated with 3 equiv of borane in tetrahydrofuran[20] at 0°. After 1 hr at 0° and 3 hr at room temperature, the organoborane was oxidized directly with chromic oxide and sulfuric acid.[18] The complex mixture obtained after work-up was purified by preparative tlc (eluent CH_2Cl_2) to yield *D*-homopregnan-20-one (5 mg), mp 165–168°.

Anal. Calcd for $C_{22}H_{36}O$: mol wt, 316; C, 83.48; H, 11.47. Found: C, 83.36; H, 11.27; M^+, 316.

D-**Homopregnan-20-one-*17a,21,21,21-d*$_4$.**—The unlabeled ketone II (5 mg) was dissolved in 4 ml of deuteriomethanol containing 1 ml of 20% sodium deuterioxide in deuterium oxide; the solution was heated overnight at reflux. The solvent was evaporated at reduced pressure and the residue redissolved in 5 ml of deuteriomethanol. After the exchange process had been repeated three times, the residue was purified by preparative tlc. The *D*-homopregnan-20-one-*17a,21,21,21-d*$_4$ isolated (3 mg, 92% d_4) exhibited melting point, tlc mobility, and vpc retention time identical with those of the unlabeled starting material II.

D-**Homoandrostan-17a-one (VI), -*18,18,18-d*$_3$ (XXVIII), -*17a,17a-d*$_2$, -*17,17-d*$_2$, *16,16-d*$_2$, *14*α-*d*$_1$, and -*3,3-d*$_2$.**—The preparation of these compounds has already been described.[12]

D-**Homoandrostan-17-one (VIII).**—The 17-ketone was isolated as a minor product in the preparation of *D*-homoandrostan-17a-one by the nitrous acid ring expansion of androstane-17-methylamino-17-ol (XXI).[12] The ketone exhibited mp 171.5–172.5°, in excellent agreement with the value already reported.[21]

Anal. Calcd for $C_{20}H_{32}O$: mol wt, 288; C, 83.27; H, 11.18. Found: C, 83.48; H, 11.08; M^+, 288.

D-**Homoandrostan-17-one-*16,16,17a,17a-d*$_4$.**—The unlabeled 17-ketone VIII was exchanged in deuteriomethanol–sodium deuterioxide–deuterium oxide in a manner described above. The product, *D*-homoandrostan-17-one-*16,16,17a,17a-d*$_4$, was isolated in high isotopic purity (80% d_4).

D-**Bishomoandrostan-17a-one (XIII) and -17b-one (XV).**—The preparation of these compounds has already been reported.[12]

D-**Bishomoandrostan-17a-one-*17,17,17b,17b-d*$_4$ and *D*-Bishomoandrostan-17*b*-one-*17a,17a-d*$_2$.**—The parent ketones were subjected to base-catalyzed exchange with deuteriomethanol–deuterim oxide in a manner analogous to that described above. The labeled ketones were isolated in high isotopic purity (80% d_4 and 98% d_2, respectively.)

Registry No.—II, 32318-95-9; II-*17a,21,21,21-d*$_4$, 32318-96-0; III, 32318-97-1; III-*16,21,21,21-d*$_4$, 32318-98-2; VI, 10147-56-5; VI-*3-d*$_1$, 32319-00-9; VI-*14*α-*d*$_1$, 32319-01-0; VI-*16,16-d*$_2$, 32319-02-1; VI-*17,17-d*$_2$, 32319-03-2; VI-*18,18,18-d*$_3$, 32319-04-3; VIII, 32319-05-4; VIII-*17,17,17b,17b-d*$_4$, 32380-94-2; XI, 32319-06-5; XV, 32319-07-6; XV-*17a,17a-d*$_2$, 32380-95-3; XV-*16*α-*d*$_1$, 32319-08-7; XVI, 32319-09-8; XVI-*3-d*$_1$, 32319-10-1; XVI-*14*α-*d*$_1$, 32319-11-2; XVI-*15*α-*d*$_1$, 32319-12-3; XVI-*16*α-*d*$_1$, 32319-13-4; 5α-pregnan-20-one, 848-62-4; 5α-androstan-17-one, 963-74-6; *D*-homo-5α-androstan-17-one, 19897-22-4.

(19) Melting points are uncorrected, and were determined in unsealed capillaries. Infrared spectra were measured in chloroform solution on a Perkin-Elmer Model 700 spectrophotometer. Nmr spectra were determined in deuteriochloroform solution with tetramethylsilane as an internal reference on a Varian T-60 spectrometer, unless otherwise indicated. Mass spectra were determined on an Atlas CH-4 spectrometer with a TO-4 ion source using the direct inlet procedure. The authors are grateful to Mr. Richard Conover for performing these measurements. All mass spectral samples were purified by preparative vpc on a Hewlett–Packard 402 gas chromatograph immediately prior to submission. Thin layer chromatography was performed on silica gel H_{254}. The elemental analyses are due to Messrs. E. Meier and J. Consul.

(20) Purchased from Ventron Corp., Beverly, Mass.

(21) D. N. Kirk, C. M. Peach, and M. P. Wilson, *J. Chem. Soc. C*, 1454 (1970).