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MASS SPECTROMETRY IN STRUCTURAL AND STEREOCHEMICAL PROBLEMS—LVI[1]

FRAGMENTATION AND HYDROGEN TRANSFER REACTIONS OF 4,4-DIMETHYL-5α-ANDROSTAN-3-ONE AND RELATED KETONES[2]

ROBERT H. SHAPIRO[3] and CARL DJERASSI
Department of Chemistry, Stanford University, Stanford, California

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Abstract—Upon electron impact, 4,4-dimethyl-5α-androstan-3-one decomposes into two major fragment ions appearing in the mass spectrum at *m/e* 175 and 216. From the spectra of several deuterated analogs of the parent ketone, both ions were shown to be hydrocarbon fragments resulting from extremely complex processes which are not susceptible to ready interpretation by the conventional principles of physical-organic chemistry. Because of the complexity of these high energy reactions, comparisons of the spectral characteristics of 4,4-dimethyl-5α-androstan-3-one were made with those of some other 4,4-dimethyl-3-ketones in order to determine the extent of fragmentation-directing influence of this moiety in the presence of a predominantly hydrocarbon environment. The results of this investigation demonstrate that the intramolecular decompositions are only partially controlled by the α-*gem*-dimethyl carbonyl grouping.

INTRODUCTION

ALTHOUGH the mass spectral behavior of steroidal ketones[4] has been shown to differ with even minor structural modifications,[5] the interest in this class of compounds lies in the elucidation of the processes by which the molecule fragments upon electron bombardment. Intensive mechanistic investigations, which employed deuterated analogs, have already been performed with steroidal ketones containing carbonyl groups at C-1,[6] C-3,[7] C-7,[8] C-11,[9] and C-16.[10] In these investigations,[6–10] most of the decomposition processes could be rationalized in terms of the physical-organic chemical principles which are usually applied to ground state reaction mechanisms. Since the 4,4-dimethyl-3-keto grouping is so common among triterpenoids, it seemed of considerable interest to examine its behavior upon electron impact and to compare it with that[7] of unsubstituted 3-keto steroids.

[1] For paper LV, Z. Pelah, D. H. Williams, H. Budzikiewicz and C. Djerassi, *J. Amer. Chem. Soc.* **86**, in press (1964).

[2] Supported in part by Grants No. CA-07195 and AM-04257 from the National Institutes of Health, U.S. Public Health Service.

[3] National Science Foundation predoctoral fellow 1963–64.

[4] H. Budzikiewicz and C. Djerassi, *J. Amer. Chem. Soc.* **84**, 1430 (1962).

[5] H. Budzikiewicz, C. Djerassi and D. H. Williams, *Interpretation of Mass Spectra of Organic Compounds*, Chap. 8. Holden-Day, San Francisco (1964).

[6] H. Powell, D. H. Williams, H. Budzikiewicz and C. Djerassi, *J. Amer. Chem. Soc.* **86**, in press (1964).

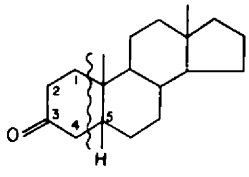
[7] R. H. Shapiro, D. H. Williams, H. Budzikiewicz and C. Djerassi, *J. Amer. Chem. Soc.* **86**, in press (1964).

[8] R. Beugelmans, R. H. Shapiro, L. J. Durham, D. H. Williams, H. Budzikiewicz and C. Djerassi, *J. Amer. Chem. Soc.* **86**, in press (1964).

[9] D. H. Williams, J. M. Wilson, H. Budzikiewicz and C. Djerassi, *J. Amer. Chem. Soc.* **85**, 2091 (1963).

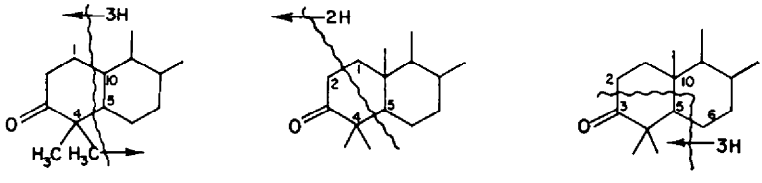
[10] C. Beard, J. M. Wilson, H. Budzikiewicz and C. Djerassi, *J. Amer. Chem. Soc.* **86**, 269 (1964).

The principal fragment ions from 5α-androstan-3-one (I) have been shown[7] to be generated by fission of the 1–10 and 4–5 bonds with charge retention by the hydrocarbon fragment. It might have been predicted that replacement of both C-4 hydrogen atoms in I by methyl groups would result in an enhancement of the above cleavages because of the more labilized penta-substituted 4–5 bond. This prediction is quite reasonable in view of the fact that 1-methyl derivatives of I show an increased ionization in the region of the spectrum corresponding to 1–10 and 4–5 bond cleavages.[7] For the 4,4-dimethyl derivative of I, the analogous ring A cleavages would result in the formation of M-99 and M-100 peaks. However, these peaks (*m/e* 203 and 202) are of minor significance in the spectrum (Fig. 1) of 4,4-dimethyl-5α-androstan-3-one (V) and, therefore, other factors which control the fragmentation processes must be considered.



I

The principal fragment ions recorded in the spectrum (Fig. 1) of the parent ketone V occur at *m/e* 175 and 216. Both these species have been shown to be hydrocarbon fragments ($C_{13}H_{19}^+$ and $C_{16}H_{24}^+$, respectively) by examination of the spectra of various labeled analogs of V. The C_{13}-fragment at *m/e* 175 must result from a complex rearrangement process which involves the fission of at least three carbon-carbon bonds and one hydrogen transfer. For the formation of the *m/e* 216 ion, three possible modes of fragmentation had to be considered: (i) fission of the 1–10 and 4–5 bonds accompanied by a methyl migration from C-4 to the hydrocarbon fragment and transfer of three hydrogen atoms to the expelled ketonic species (*a*); (ii) fission of the 1–2 and 4–5 linkages with concomitant migration of two hydrogen atoms to the oxygen-containing fragment (*b*); and (iii) fission of the 2–3, 5–10 and 5–6 bonds accompanied by the transfer of three hydrogen atoms (*c*).



(*a*) (*b*) (*c*)

Because of the complexity of the fragmentation reactions of V, we compared its behavior with some other polycyclic ketones containing a similar α-*gem*-dimethyl moiety in order to determine whether the same phenomena occurred during electron bombardment of such related compounds as 1,1,10-trimethyl-2-decalone,[11] lanostan-3-one (XXII) and 4,4-dimethylcholestan-3-one (XXIII).

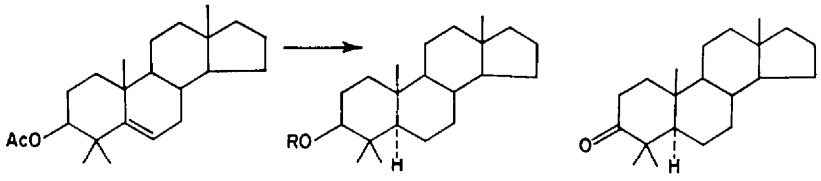
[11] E. Lund, H. Budzikiewicz, J. M. Wilson and C. Djerassi, *J. Amer. Chem. Soc.* **85**, 1528 (1963).

The results of this investigation demonstrate that the fragmentation-directing influence of the α-*gem*-dimethyl ketone moiety decreases with increasing hydrocarbon environment.

RESULTS AND DISCUSSION

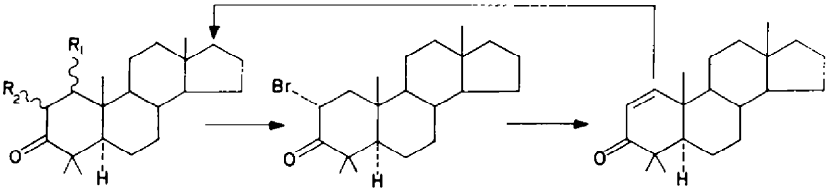
Syntheses of 4,4-*dimethyl*-5α-*androstan*-3-*ones*

4,4-Dimethyl-5α-androstan-3β-ol (IV) was prepared from 4,4-dimethyl-Δ⁵-androsten-3β-ol acetate (II)[8] by hydrogenation to the saturated analog III followed by saponification. Subsequent oxidation of the alcohol IV led to the parent ketone V.



II III R=Ac IV R=H V

Bromination of V gave the 2-bromo derivative VI, in which the bromine atom was proven to be equatorial[12] by optical rotatory dispersion[13] measurements. Dehydrohalogenation of VI to the enone VII, followed by catalytic deuteriation afforded the 1,2-d_2-analog VIII, which was back-exchanged at C-2 to give the 1-d_1-derivative IX. The configuration of the heavy isotopes in both VIII and IX remains unknown. The α-configuration would be expected if ring A in enone VII were in a chair-like conformation. If ring A has more boat-like character then the C-4 axial methyl group may hinder hydrogenation from the rear side.



V $R_1 = R_2 = H$
VII $R_1 = R_2 = D$
IX $R_1 = D, R_2 = H$

VI VII

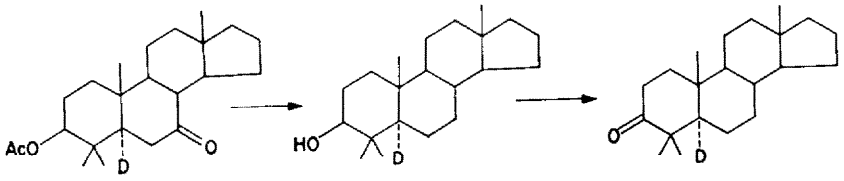
The preparation of 4,4-dimethyl-5α-d_1-androstan-3β-ol-7-one acetate (X) has been described previously.[8] Its conversion into the 5α-d_1-3-ketone XII was effected by Huang-Minlon reduction[14] and subsequent Jones oxidation.[15]

[12] Bromination of 4,4-dimethylcholestan-3-one under thermodynamic conditions gives the 2α-bromo ketone in which the bromine atom is equatorial. Therefore, ring A must be in the chair conformation. See I. Malunowicz, *Bull. Acad. Polon. Sci. Ser. Sci. Chim.* **10**, 311 (1962); and A. Lablache-Combier, J. Levisalles, J.-P. Pete and H. Rudler, *Bull. Soc. Chim. Fr.* 1689 (1963).

[13] C. Djerassi, *Optical Rotatory Dispersion* Chap. 9. McGraw-Hill, New York (1960).

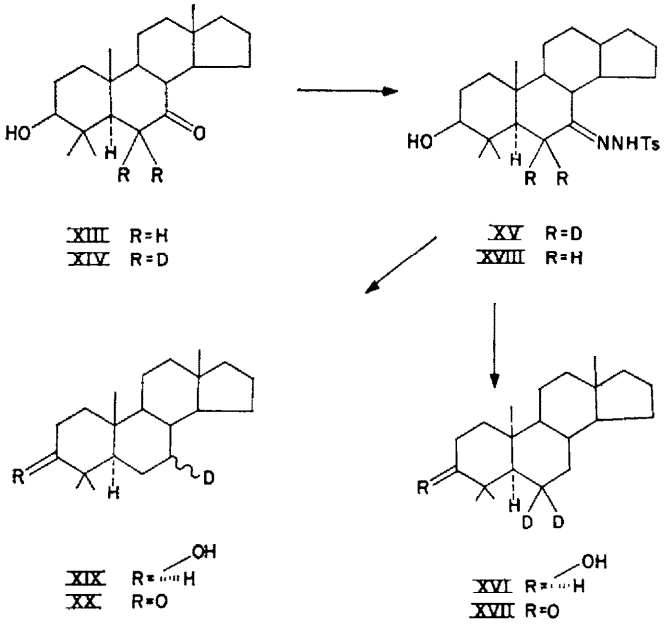
[14] Huang-Minlon, *J. Amer. Chem. Soc.* **68**, 2487 (1946).

[15] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. Weedon, *J. Chem. Soc.* 39 (1964).



X XI XII

4,4-Dimethyl-5α-androstan-3β-ol-7-one (XIII)[8] was subjected to base-catalyzed equilibration in deuteriomethanol for five days, a treatment which resulted in the introduction of predominantly 2 deuterium atoms. Since earlier studies[8] had demonstrated that the order of deuterium introduction was 6α and 6β ≫ 8β, the resulting product is largly the 6,6-d_2-7-ketone XIV. Conversion to the corresponding tosylhydrazone XV and reduction[16] with lithium aluminum hydride, followed by oxidation of the alcohol XVI, led to the ketone XVII, which was composed of 76% d_2- and 24% d_3-species. This isotopic distribution did not, however, affect the calculations because the 8β-hydrogen atom was not involved in the migration process (Table 1) and acted merely as a label for the hydrocarbon portion of the molecule.



XIII R=H
XIV R=D

XV R=D
XVIII R=H

XIX R=α-H
XX R=O

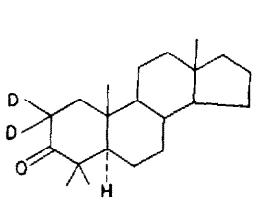
XVI R=α-H
XVII R=O

Labeling of C-7 was effected by a similar procedure to that outlined above. The unexchanged ketone XIII was converted to its tosylhydrazone XVIII, which was then reduced with lithium aluminum deuteride and the resulting alcohol XIX transformed into the ketone XX.

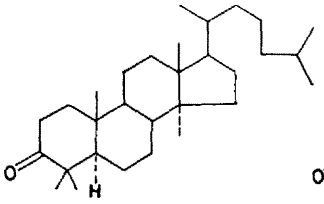
2,2-d_2-4,4-Dimethyl-5α-androstan-3-one (XXI) was prepared by base-catalyzed

[16] L. Caglioti and M. Magi, *Tetrahedron* **19**, 1127 (1963).

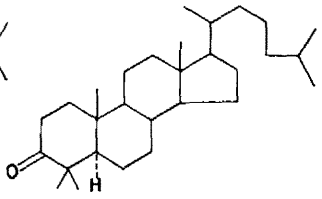
equilibration of the parent ketone V in deuteriomethanol–deuterium oxide. Lanostan-3-one (XXII)[17] and 4,4-dimethylcholestan-3-one (XXIII)[18] were prepared according to literature procedures from Δ^8-lanosten-3β-ol-7,11-dione acetate[19] and cholesterol, respectively.



XXI



XXII



XXIII

Mass spectrum of 4,4-*dimethyl-5α-androstan-3-one*(V)

The mass spectrum of 4,4-dimethyl-5α-androstan-3-one (V), reproduced in Fig. 1, shows two principal fragment ions in the high mass range at *m/e* 216 (process A) and *m/e* 175 (process B). The corresponding *m/e* values for processes A and B obtained

TABLE 1. FRAGMENT IONS FROM LABELED ANALOGS OF 4,4-DIMETHYL-5α-ANDROSTAN-3-ONE (V)[a]

4,4-Dimethyl-5α-androstan-3-one		*m/e* values for process		
		Isotopic purity	A	B
d_0	(V)	—	216	175
2,2-d_2	(XXI)	85%	216	175
1,2-d_2	(VIII)	87%	217	175
1-d_1	(IX)	94%	217	175
5α-d_1	(XII)	55%	216 (100%)	175
6,6-d_2	(XVII)	64%[b]	217 (50%) 218 (50%)	177
7ξ-d_1	(XX)	92%	217	176
17β-OH		—	232[c]	191[c,d]

[a] Corrected for natural abundance of ^{13}C and isotopic contaminants.

[b] Contained 24% d_3; subtracted by assuming 0·5 hydrogen atom transfer from C-6 and 0·0 from C-8 during process A. The lack of participation of the 8β-hydrogen atom was indicated by the abundance of the *m/e* 219 peak which was 22% of the total ionization in this area. The *m/e* 178 peak was also increased by the amount of the contaminant.

[c] 16 mass unit increment due to hydroxyl group.

[d] An intense *m/e* 173 peak is due to the loss of water from *m/e* 191.

from the spectra of the labeled analogs of V are recorded in Table 1. It can be seen from these values that both major fragments are hydrocarbon ions, i.e. both fragmentations A and B occur with the expulsion of an oxygen-containing neutral species.

[17] W. Voser, M. Montavon, H. H. Günthard, O. Jeger and L. Ruzicka, *Helv. Chim. Acta* **33**, 1893 (1950).

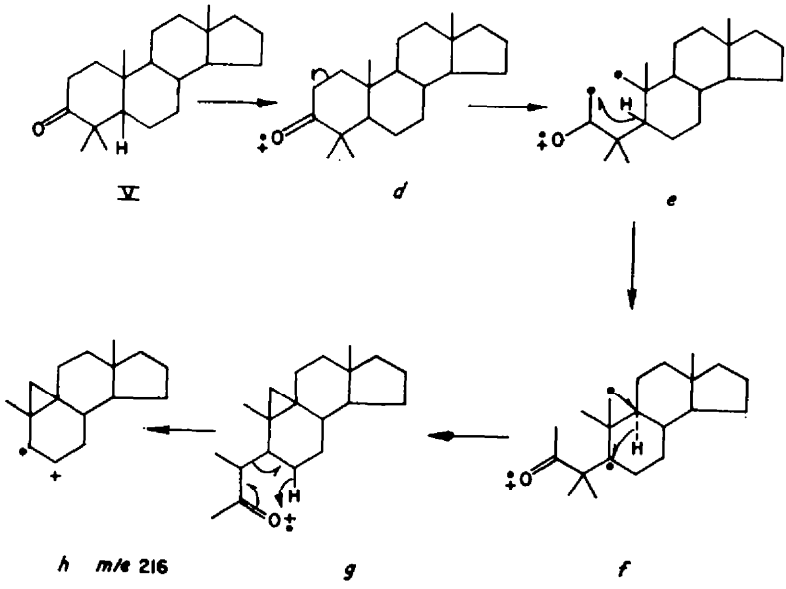
[18] J. L. Beton, T. G. Halsall, E. R. H. Jones and P. C. Phillips, *J. Chem. Soc.* 753 (1957).

[19] We wish to express our gratitude to Professor G. R. Pettit, University of Maine, for a gift of this material.

(A) *M*-86 (*m/e* 216) *ion.* As mentioned in the introduction, there are three possibilities for the expulsion of a $C_5H_{10}O$ neutral fragment. The *m/e* values in Table 1 show that the C-2 hydrogen atoms are lost while the one attached to C-1 is retained by the charge-bearing species. If the cleavage shown in (*a*) is operative, then the C-1 hydrogen atom must be moved to the hydrocarbon portion. Such a possibility is extremely unlikely, since four hydrogen atoms would have to be transferred to the expelled portion in order to correspond to a net loss of three hydrogens in process (*a*).

The fragmentation represented formally in (*b*) is much more plausible since scission of the 1–2 bond would result in concomitant loss of the C-2 hydrogen atoms and retention of the one attached to C-1. However, this process would involve the quantitative transfer of the 5α-hydrogen atom and cleavage of the 4–5 linkage, i.e. two C-5 bonds would have to be broken. Although instances have been reported,[6,7] in which two bonds connected to one carbon atom are severed, none has been accompanied by the complete transfer of its attached hydrogen atom. If the cleavages represented in (*b*) occur, the 50% of the second migrating hydrogen atom originates from C-6 (Table 1). The bond ruptures shown in (*c*) require that the hydrogen atoms connected to C-2 and C-6 migrate even though they are attached to sites which also undergo carbon-carbon cleavage. In addition, since three carbon-carbon bonds and the same number of carbon-hydrogen linkages must be severed in (*c*), this formal representation appears untenable.

The fact that the *m/e* 216 ion is formed, at least in part, directly from the molecular ion is ascertained by the occurrence of a metastable peak at *m/e* 154·5 in the spectrum

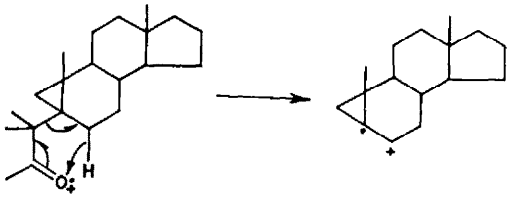


of V. Fragmentation (*b*) involving the fission of the 1–2 and 4–5 bonds with concomitant hydrogen transfer from C-5 and C-6 is thus the most reasonable representation for the formation of the M-86 ion. While speculative and *a priori* not predictable, we propose the following mechanism for the genesis of the M-86 species.

The driving force for the initial 1–2 bond cleavage in *d* is not apparent; however

the sequence which follows the primary bond rupture rationalizes the formation of the product *h* quite well. After migration of the C-5 hydrogen to C-2 in *e*, the intra-species rearrangement in *f* is invoked in order to allow for eventual cleavage of the 4–5 bond without involving fission at a vinylic center. Although the hydrogen atom attached to C-9 is arbitrarily chosen to saturate C-5, the process $f \rightarrow g$ appears rather plausible. Fission of the 4–5 bond with accompanying hydrogen transfer from C-6 can then occur *via* the six-membered cyclic transition state as shown in *g*. Species *h* is predicted to be stable, since the ionized double bond[20] is in conjugation with cyclopropane ring.

Alternatively, the C-5 hydrogen transfer (*e*) may not be accompanied by rearrangement of the C-9 hydrogen atom (*f*), in which case species *g'* would be obtained directly. Subsequent migration of the C-6 hydrogen atom would then yield *h'* (*m/e* 216)—a sequence which is still consistent with the deuterium labeling results.



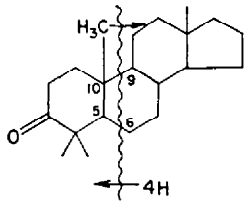
g' *h'* *m/e* 216

(B) *M*-127 (*m/e* 175) *ion*. The most abundant fragment (*m/e* 175) in the spectrum (Fig. 1) of 4,4-dimethyl-5α-androstan-3-one (V), also arises from a one-step decomposition of the molecular ion as indicated by a metastable peak at *m/e* 101·2. Since the data collected in Table 1 requires that the *m/e* 175 ion be $C_{13}H_{19}^+$, at least three carbon-carbon and one carbon-hydrogen linkages must be broken. The *m/e* values in Table 1 indicate that C-1, C-2 and C-5 are probably lost, while C-6, C-7 and C-17 are retained by the charge-bearing species. Consequently, the implication that scission of the 5–6 linkage occurs is very strong and if we assume that homolysis of this bond takes place, then only two formal representations seem possible: Fission (*i*) of the 5–6 and 9–10 bonds with transfer of the angular methyl group to the hydrocarbon portion and simultaneously migration of four hydrogen atoms to the oxygen-bearing species. Since none of these hydrogen atoms originated at C-6, C-7 or C-8 (Table 1), this process seemed so unreasonable that no attempt was made to label the alleged migrating angular methyl group attached to C-10. The alternative fragmentation (*j*) which involves fission of the 5–6 bond also implicates cleavage of the 5–10 and 1–10 bonds with the transfer of the angular methyl group and one hydrogen (not from C-6, C-7 or C-8) to the expelled fragment.

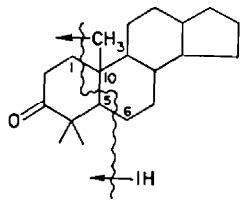
Both of these fragmentations appear untenable because seven and five bonds, respectively, have to be broken during the one-step processes. Moreover, three of the bonds connected to C-10 are cleaved in the process represented by (*j*).

A third possible, yet seemingly unreasonable, process is represented in (*k*) with

[20] J. S. Shannon, *Austral. J. Chem.* **16**, 683 (1963).

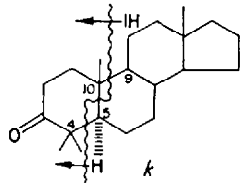


i



j

rearrangement of two hydrogen atoms. In this formulation, three bonds connected to C-5 are broken and the 5α-hydrogen must transfer completely. If we assume that only process (*j*) or (*k*) is operative, they can clearly be distinguished only by labeling C-5 with ^{13}C, a project that we have not undertaken.



k

These three representations (*i*, *j* and *k*) have been presented as a means of demonstrating the remarkable complexity of the process leading to the most abundant ion in the spectrum (Fig. 1) of 4,4-dimethyl-5α-androstan-3-one (V). There is no doubt that in this case the principles normally used to rationalize ground state reactions do not apply.

Mass spectra of other 4,4-dimethyl-3-ketones

In Table 2 are shown the abundances of the ions formed during process A (*m/e* 216 in V) and B (*m/e* 175 in V) for 1,1,10-trimethyl-2-decalone,[11] lanostan-3-one (XXII) and 4,4-dimethylcholestan-3-one (XXIII) as compared with those shown for 4,4-dimethyl-5α-androstan-3-one (V) in Fig. 1.

TABLE 2. INTENSITIES OF M-86 AND M-127 PEAKS[a]

Ketone	Mol. wt	M-86 Ion	M-127 Ion
4,4-Dimethyl-5α-androstan-3-one (V)	302	38	100
4,4-Dimethylcholestan-3-one (XXIII)	414	4	16
Lanostan-3-one (XXII)	428	1	7
1,1,10-Trimethyl-2-decalone[11]	194	70	50

[a] Expressed as percent of the abundance of the most intense peak in the corresponding spectrum.

It can be seen from the figures in Table 2 that the M-86 ion decreases continuously with increasing hydrocarbon environment, while the M-127 fragment goes through a maximum, appearing as the most intense peak in Fig. 1 and then decreasing. The C_8 side chains in both lanostan-3-one (XXII) and 4,4-dimethylcholestan-3-one (XXIII) apparently direct the fragmentation courses of these molecules far more than does the

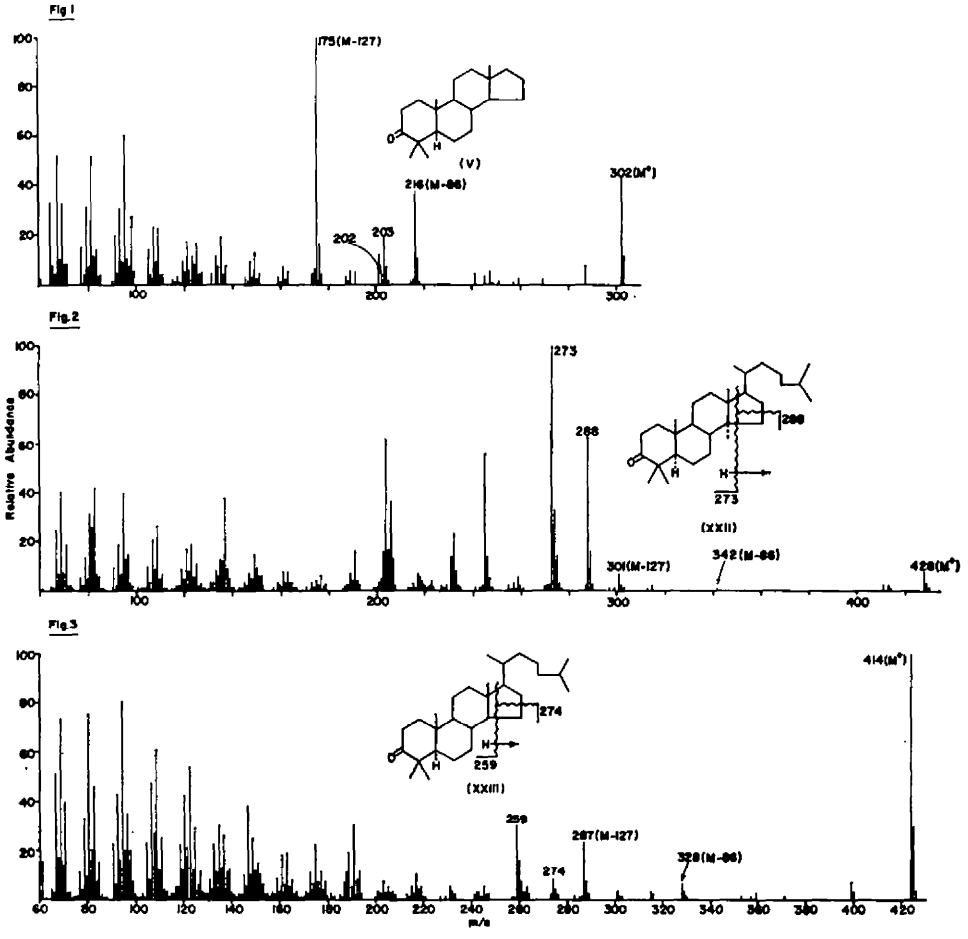


FIG. 1. Mass spectrum of 4,4-dimethyl-5α-androstan-3-one.

FIG. 2. Mass spectrum of lanostan-3-one.

FIG. 3. Mass spectrum of 4,4-dimethylcholestan-3-one.

α-*gem*-dimethyl carbonyl grouping. In fact, the C-14 methyl group of XXII enhances the ring D cleavage to such an extent that the ion formed during the fragmentation (*m/e* 273) becomes the base peak (Fig. 2). The molecular ion (*m/e* 414) formed from 4,4-dimethylcholestan-3-one (XXIII) shown in Fig. 3 is apparently very much more stable than its 14α-methyl homolog XXII and thus, fragmentation in the high-mass region of the spectrum is not nearly as extensive. Nevertheless, the most abundant fragment in the high mass region of Fig. 3 results from 13–17 and 14–15 bond cleavages accompanied by migration of one hydrogen atom to the expelled hydrocarbon species. The *m/e* 67 ion in the spectrum[11] of 1,1,10-trimethyl-2-decalone does not necessarily correspond to the *m/e* 175 ion (Fig. 1) of 4,4-dimethyl-5α-androstan-3-one (V), even though both species occur at M-127. The $C_5H_7^+$ cation is an abundant species in the spectra[11] of all β-decalones regardless of methyl substitution and has been shown[11] to

arise from several different processes. Therefore, the fragment expelled from the α-*gem*-dimethyl decalone may bear no resemblance to that lost from 4,4-dimethyl-5α-androstan-3-one (V). The M-86 fragment, however, probably owes its genesis to the identical process in the steroid and decalone series.

CONCLUSION

Although it has been shown by several investigations[6–10] that the mass spectra of steroidal ketones do not lend themselves to wide generalizations, the elucidation of their decomposition routes, induced by electron impact, is still very intriguing. In view of the results of the present investigation, some caution must be exercised in applying the physical-organic principles of ground state reaction mechanisms to these high energy processes. The ground state rules, however, do seem to apply to certain classes of steroids, such as ethylene ketals[1,21] and amines[22] where charge localization in the molecular ion is greatly favoured.

EXPERIMENTAL[23]

4,4-*Dimethyl*-5α-*androstan*-3β-*ol acetate* (III). A solution of II[8] (680 mg) in ethanol (25 ml) containing 10% Pd–C (100 mg) was stirred in an H_2 atmosphere for 8 hr. During this time, 50·0 ml H_2 was absorbed (theoretical uptake 49·0 ml) and no further absorption was noted during an additional 0·5 hr. Removal of the catalyst by filtration and evaporation of the filtrate at red. press. gave a white crystalline residue. Recrystallization of the residue from ethanol gave the saturated acetate III (650 mg, 96%) as fine crystals, m.p. 121–122·5°, $[\alpha]_D^{26}$ −5·2° (*c*, 1·16), $\nu_{max}^{CHCl_3}$ 1710 and 1250 cm.$^{-1}$ (Found: C, 79·61; H, 11·02; mol. wt, 346 (M-60 ion at *m/e* 286 in mass spectrum). $C_{23}H_{38}O_2$ requires: C, 79·71; H, 11·05%; mol. wt, 346).

4,4-*Dimethyl*-5α-*androstan*-3β-*ol* (IV). A suspension of the acetate III (458 mg) in methanol (15 ml) containing previously dissolved KOH (175 mg) was heated to boiling. After a few min the reaction mixture became homogeneous and heating under reflux was continued for an additional 1·5 hr. Upon cooling to room temp, a white crystalline solid separated and was collected by filtration, washed with water and dried in air. Recrystallization from methanol gave the alcohol IV (330 mg, 83%), m.p. 160–161° (transition at 119–120°), $[\alpha]_D^{25}$ −17·2° (*c*, 0·93). (Found: C, 80·87; H, 12·04; mol. wt 304 (mass spec.). $C_{21}H_{36}O$ requires: C, 82·83; H, 11·92%; mol. wt 304; $C_{21}H_{36}O$-$\frac{1}{2}CH_3OH$ requires: C, 80·56; H, 11·95%).

4,4-*Dimethyl*-5α-*androstan*-3-*one* (V). To a solution of IV (3·00 g) in reagent grade acetone (250 ml) blanketed with a N_2 atmosphere, was added dropwise 8N CrO_3 solution until the supernatant liquid remained yellow for 3 min. Excess anhydrous $MgSO_4$ was added to remove the residual water. The suspension was filtered and the filtrate evaporated to dryness at red. press. leaving a slightly yellow crystalline residue. Recrystallization of the residue from methanol gave the ketone V (2·93 g, 98%) as large flat plates, m.p. 121–122°. Several additional recrystallizations from the

[21] [a] G. v. Mutzenbecher, Z. Pelah, D. H. Williams, H. Budzikiewicz and C. Djerassi, *Steroids* **1**, 475 (1963); [b] H. Audier, A. Diara, M. J. Durazo, M. Fetizon, P. Foy and W. Vetter, *Bull. Soc. Chim. Fr.* 2827 (1963).

[22] [a] W. Vetter, P. Longevialle, P. Khuong-Huu-Lainé, Q. Khuong-Huu and R. Goutarel, *Bull. Soc. Chim. Fr.* 1324 (1963); [b] L. Dolejš, V. Hanuš, V. Černy and F. Šorm, *Collect. Czech. Commun.* **28**, 1584 (1963); [c] Z. Pelah, M. A. Kielczewski, J. M. Wilson, M. Ohashi, H. Budzikiewicz and C. Djerassi, *J. Amer. Chem. Soc.* **85**, 2470 (1963).

[23] Routine m.p were taken in capillary tubes and are uncorrected, while those for analytical samples were determined on a Kofler hot stage and are corrected. Rotations were determined in chloroform solution. All mass spectra were measured with a Consolidated Electrodynamics Corp. mass spectrometer No. 21-103C using an all-glass inlet system heated to 200°, while the isatron temp was maintained at 270°. The ionizing energy was kept at 70 ev. and the ionizing current at 50 μa. Analytical thin-layer chromatoplates had a thickness of 0·25 mm of silica gel G (E. Merck A. G., Darmstadt) and the spots were detected by spraying with 2% ceric sulfate solution in 2N H_2SO_4.

same solvent gave an analytical sample, m.p. 121–122°, $[\alpha]_D^{25}$ −25·8° (*c*, 1·08), $\nu_{max}^{CHCl_3}$ 1688 cm.$^{-1}$ The optical rotatory dispersion curve showed two Cotton effects, probably due to asymmetric solvation:[24] $[\alpha]_{589}$ −41°, $[\alpha]_{330}$ −237° (trough), $[\alpha]_{302}$ −102° (peak), $[\alpha]_{298}$ −164° (trough), $[\alpha]_{293}$ +61° (peak), (C, 0·126 in methanol). (Found: C, 83·32; H, 11·31; mol. wt 302 (mass spec.). $C_{21}H_{34}O$ requires: C, 83·38; H, 11·33%; mol. wt, 302).

2α-*Bromo*-4,4-*dimethyl*-5α-*androstan*-3-*one* (VI). To a stirred solution of V (269 mg) in acetic acid (15 ml) was added pyridine hydrobromide perbromide[25] (292 mg) in small portions during 15 min. After the addition was complete, the slightly yellow solution was allowed to stir at room temp for an additional 30 min, during which time a portion of the product crystallized. Water (3 ml) was added and the separated solid was collected by filtration, washed with water and dried in air. The white granules (282 mg) obtained by filtration were recrystallized from ethanol–chloroform giving the bromo ketone VI (242 mg, 72%) as white granules m.p. 182–183° (sinters at 123°) $[\alpha]_D^{29}$ −30·6° (*c*, 1·05), $\nu_{max}^{CHCl_3}$ 1709 cm^{-1}. As in the case of the parent ketone V, the rotatory dispersion curve of VI showed two extrema: $[\alpha]_{589}$ −32°, $[\alpha]_{360}$ −70° (trough), $[\alpha]_{329}$ −64° (peak), $[\alpha]_{290}$ −434° (trough), $[\alpha]_{262}$ −256° (peak), (*c*, 0·155 in methanol). (Found: C, 66·26; H, 8·80; Br, 20·70. $C_{21}H_{33}BrO$ requires: C, 66·13; H, 8·72; Br, 20·95%).

4,4-*Dimethyl*-Δ^1-5α-*androsten*-3-*one* (VII). To a boiling suspension of $CaCO_3$ (200 mg) in N,N-dimethylacetamide[26] (7 ml) was added the bromo ketone VI (242 mg) and the mixture allowed to reflux for 45 min. After cooling to room temp, the suspension was poured into 5% HCl aq (25 ml). The organic precipitate was partitioned into ether and the ethereal solution was washed with water, dried over $MgSO_4$ and evaporated to dryness. The crystalline residue was recrystallized from methanol giving the Δ^1-3-ketone, m.p. 112–114°, $[\alpha]_D^{27}$ ±0° (*c*, 0·99), λ_{max}^{EtOH} 229 mμ (log ε 4·35), ν_{max}^{CHCl} 1648 cm^{-1}. (Found: C, 83·85; H, 10·63; mol. wt, 300 (mass spec.). $C_{21}H_{32}O$ requires: C, 83·94; H, 10·73%; mol. wt, 300).

1ξ,2ξ-d_2-4,4-*Dimethyl*-5α-*androstan*-3-*one* (VIII). In a microhydrogenation apparatus, a solution of VII (14 mg) in cyclohexane (3 ml) containing 10% Pd–C (15 mg) was allowed to stir in an atmosphere of deuterium gas at 20°. In about 1 min, exactly one equiv. (1·15 ml) deuterium had been absorbed and no further uptake was noted during an additional 4 min. A thin-layer chromatogram, developed with benzene–ethyl acetate (9:1), showed a single spot with an R_f corresponding to that of the unlabeled parent ketone V. The catalyst was removed by filtration and the filtrate was evaporated to dryness at red. press. leaving a crystalline residue (13 mg), m.p. 120–122°. Mass spectral analysis showed this material to be of 87% isotopic purity; the remaining 13% was the d_1-species.

1ξ-d_1-4,4-*Dimethyl*-5α-*androstan*-3-*one* (IX). To the dried residue VIII was added 5% methanolic NaOH aq (3 ml) and the mixture was heated to boiling on a steam bath. Water was added to incipient turbidity and the solution was heated under reflux for 1 hr. Cooling to room temp afforded crystals (9 mg) which were collected by filtration, washed with water and dried in air. This material, m.p. 119–121°, was shown to have an isotopic distribution of 6% d_0 and 94% d_1.

5α-d_1-4,4-*Dimethylandrostan*-3β-*ol* (XI). A mixture of X (96 mg), diethylene glycol (15 ml), n-butyl alcohol (4 ml) and 95% anhydrous hydrazine (3 ml) was heated at reflux temp (142°) for 1·5 hr. Potassium hydroxide (600 mg) was added and the solvents were codistilled until the reaction temp reached 200°. Heating at this temp was continued for 4 hr. After cooling to 50°, the straw colored solution was poured into water (75 ml) and the resulting suspension extracted with three 20 ml portions of ether. The organic layer was washed with dil. HCl aq, then water, dried over $MgSO_4$ and evaporated to dryness. The crude crystalline residue (80 mg, 87%), m.p. 158–160°, showed no carbonyl band in the IR and one spot in a thin-layer chromatogram, developed with benzene–ethyl acetate (9:1), with an R_f identical to that exhibited by unlabeled alcohol IV. This material was used in the next step without further purification.

5α-d_1-4,4-*Dimethylandrostan*-3-*one* (XII). A Jones oxidation[15] exactly as described for the conversion of IV to V, was used to prepare the 5α-d_1-3-ketone XII from the corresponding alcohol XI. The ketone XII, m.p. 119–120°, had an isotopic purity of 54%; the remainder of the material was the parent ketone V. The poor isotopic purity of this material did not affect the interpretation of the mass spectrum of XII, since the major fragment ions appeared completely at *m/e* 175 and 216.

6,6-d_2-4,4-*Dimethyl*-5α-*androstan*-3β-*ol*-7-*one tosylhydrazone* (XV). A clean piece of Na (100 mg)

[24] A. Moscowitz, K. M. Wellman and C. Djerassi, *Proc. Natl. Acad. Sci. U.S.* **50**, 799 (1963).
[25] C. Djerassi and C. R. Scholz, *J. Amer. Chem. Soc.* **70**, 417 (1948).
[26] G. F. H. Green and A. G. Long, *J. Chem. Soc.* 2532 (1961).

was dissolved in deuteriomethanol (10 ml) and after the evolution of deuterium had subsided, XIII[8] (200 mg) was added and the resulting solution heated to boiling. External heating was discontinued while deuterium oxide (ca. 1·5 ml) was added to incipient turbidity and then the mixture was heated at reflux temp for 120 hr. The host solution was added to a mixture of *p*-toluenesulfonyl hyrazine (300 mg) in deuterium oxide (3 ml) containing acetyl chloride (2 drops). Within 1 min, a heavy precipitate formed which was collected by filtration and washed well with water. After drying over Drierite at 0·1 mm, the material (315 mg) was used in the next step without purification.

The undeuteriated analog XVIII was prepared from unexchanged 7-keto-3-alcohol XIII in the same way as outlined above. Methanol was used as the solvent and conc. HCl aq was used as the acid catalyst. The unlabeled tosylhydrazone XVIII decomposed without melting at 228°.

6,6-d_2-4,4-*Dimethyl-5α-androstan*-3-*one* (XVII). To a suspension of $LiAlH_4$ (200 mg) in dioxane (25 ml, freshly distilled from $LiAlH_4$) was added the tosylhydrazone XV (200 mg) and the mixture heated under reflux for 12 hr in an apparatus protected from atmospheric moisture. The mixture was cooled to 10°, the excess hydride was decomposed with a sat. Na_2SO_4 aq and the residual water was removed with the aid of anhydrous $MgSO_4$. After removal of the inorganic material by filtration, the filtrate was evaporated to dryness giving a colorless oil. The oil was adsorbed on neutral alumina (10 g, activity II) and eluted with benzene, giving the alcohol XVI, m.p. 158–160°. Without purification, the 6,6-d_2-alcohol XVI was oxidized to the corresponding ketone XVII by the procedure of Jones *et al.*[15] The compound (XVII) thus obtained contained the following isotopic distribution: 12% d_1, 64% d_2, and 24% d_3.

7ξ-d_1-4,4-*Dimethyl-5α-androstan*-3-*one* (XX). The tosylhydrazone XVIII was reduced with $LiAlD_4$ in dioxane as described above for the reduction of XV with hydride. The alcohol XIX was purified by column chromatography and oxidized to the ketone XX with chromic acid. The isotopic purity of the contaminants were 4% d_0 and 4% d_2.