[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY, STANFORD, CALIF.]

Mass Spectrometry in Structural and Stereochemical Problems. LV.[1] The Mass Spectrometric Fragmentation of Ethylene Ketals[2]

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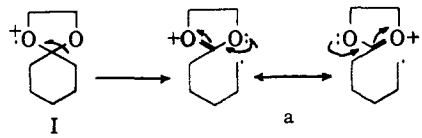
The mass spectra of a wide variety of steroidal and triterpenoid ethylene ketals have been studied. The results indicate that this function strongly directs bond fission thus permitting the location of functional groups and other nuclear substituents. Special attention is called to the use of this mass spectrometric fragmentation behavior for locating the site of alkylation in 3-keto steroids. Deuterium labeling was employed to substantiate some of the mechanistic proposals made in this paper.

Introduction

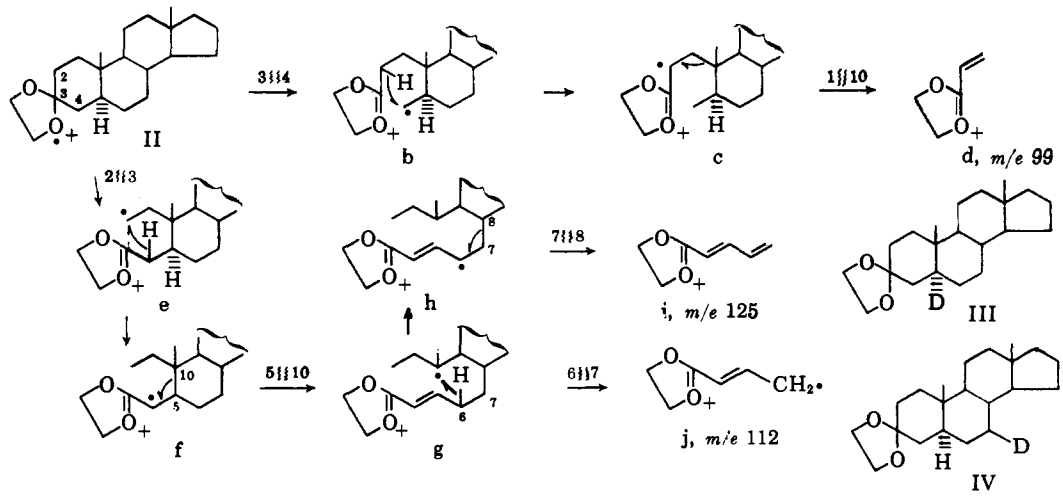
It has previously been pointed out that ethylene ketals,[3-5] ethylene thioketals,[3,4] and dimethylamino compounds[3,6-8] are desirable derivatives for mass spectrometric purposes. We have now extended our initial studies[4] on ethylene ketals and thioketals, and as a result have concluded that the former derivative is far superior to its sulfur analog for the purpose of directing fragmentation in a predictable manner. Moreover, the ethylene ketal function is more easily introduced[9]



I a

than the dimethylamino group and consequently is the derivative of choice. Steroids, being natural products which do not normally contain centers facilitating highly selective fragmentation,[10,11] are therefore discussed in this paper in terms of the mass spectra of their ethylene ketal derivatives, the results for two ketals of the triterpene series being also included.

Before discussing specific cases, it should be pointed out that the ability of a heteroatom to stabilize a positive charge and hence direct fragmentation in a predictable manner will increase with increasing strength of the substituent as a Lewis base. Such a relationship is borne out by the mass spectra of steroidal amines,[3,6-8] in which certain immonium ions carry a very large percentage of the total ion current. While ethers are not as strong Lewis bases as amines, the presence of two adjacent heteroatoms in ethylene ketals results in resonance stabilization of the positive charge between the two oxygen atoms. This resonance can occur in the molecular ion of a cyclic ethylene ketal (I) after homolysis of a carbon–carbon bond adjacent to the functional group (a).[12]



Discussion of Mass Spectral Fragmentation Processes

3-Ethylene Ketals.—Since the presence of an oxygen function at C-3 is usual in steroids and triterpenes, it is of great importance that cleavages characteristic of 3-ethylene ketals be well documented and mechanistically clear. The mass spectrum (Fig. 1) of 5α-androstan-3-one ethylene ketal (II) has been

(1) Paper LIV: P. Brauchli, V. Deulofeu, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 1895 (1964).

(2) Financial support by the National Institutes of Health (Grants No. GM-06840, CA-07195, and AM-04257) is gratefully acknowledged.

(3) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, San Francisco, Calif., 1964, pp. 54–58 and 74–80.

(4) G. von Mutzenbecher, Z. Pelah, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *Steroids*, **2**, 475 (1963).

(5) H. Audier, A. Diara, M. de J. Durazo, M. Fétizon, P. Foy, and W. Vetter, *Bull. soc. chim. France*, 2827 (1963).

(6) W. Vetter, P. Longevialle, F. Khuong-Huu-Laine, Q. Kuong-Huu, and R. Goutarel, *ibid.*, 1324 (1963).

(7) L. Dolejš, V. Hanuš, V. Cerný, and F. Šorm, *Collection Czech. Chem. Commun.*, **28**, 1584 (1963).

(8) Z. Pelah, M. A. Kielczewski, J. M. Wilson, M. Ohashi, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2470 (1963).

(9) J. W. Keana in (C. Djerassi, Ed.) "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963, Chapter 1.

(10) H. Powell, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 2623 (1964).

(11) R. H. Shapiro, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *ibid.*, **86**, 2837 (1964).

(12) In publications from this laboratory, a full arrow (→) represents a two-electron movement; the shift of one electron in a homolytic fission is indicated by a fishhook (⇀). Implicit in the latter convention is that the other electron in the bond is shifted in the opposite direction (see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry; Vol. I—Alkaloids," Holden-Day, San Francisco, Calif., 1964, p. 2.

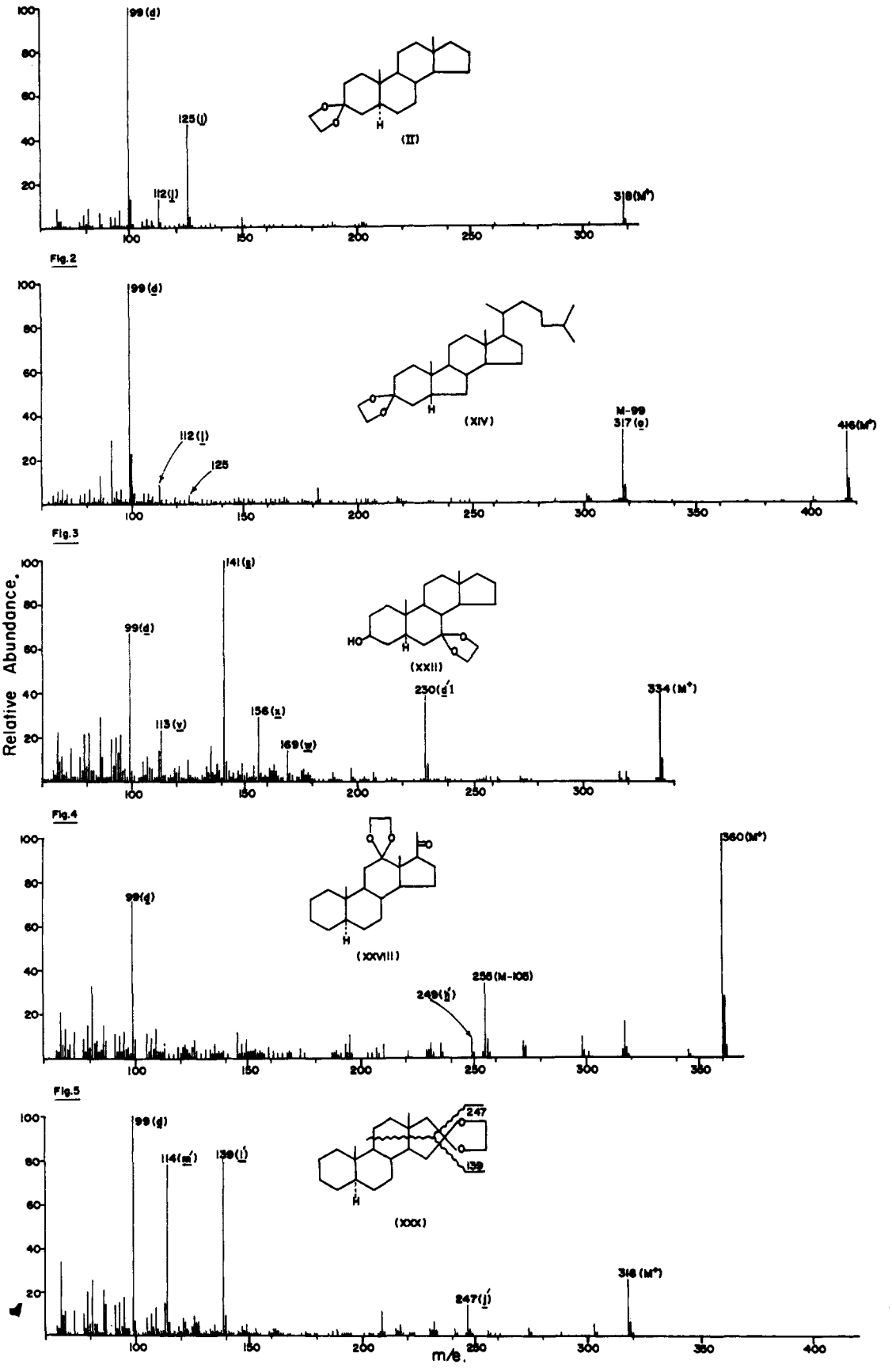


Fig. 1.—Mass spectrum of 5α-androstan-3-one ethylene ketal (II).
Fig. 2.—Mass spectrum of β-norcoprostan-3-one ethylene ketal (XIV).
Fig. 3.—Mass spectrum of 5α-androstan-3β-ol-7-one ethylene ketal (XXII).
Fig. 4.—Mass spectrum of 5α-pregnane-12,20-dione 12-ethylene ketal (XXVIII).
Fig. 5.—Mass spectrum of 5α-androstan-16-one ethylene ketal (XXX).

discussed previously[3-5] and the sequences leading to the ions *m/e* 99 (d), 125 (i), and 112 (j) are outlined only because of their basic relevance to the ensuing discussion. In the cases of the exactly analogous cleavages of ethylene thioketals[4] and dimethylamines,[8] all the proposed hydrogen transfers have been substantiated by deuterium labeling.

These cleavages are also supported by the spectra of deuterated analogs of II. Thus, in the spectrum of the 5α-d_1-derivative III, the *m/e* 99 ion (d) is unmoved, while *m/e* 112 (j) and 125 (i) shift to *m/e* 113 and 126, respectively (see Table I). The 7β-d_1-compound IV exhibits these ions at *m/e* 99, 112, and 126, exactly as expected (Table I).

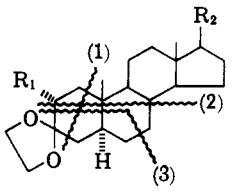
TABLE I

THE *m/e* VALUES OF IONS ARISING BY CLEAVAGES (1), (2), AND (3) IN 3-ETHYLENE KETALS (SEE IIa)

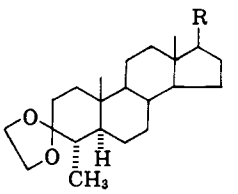
Compound	(1)	(2)	(3)
		m/e values	
II	99 (100)	125 (46)	112 (13)
III	99 (100)	126 (49)	113 (9)
IV	99 (100)	126 (40)	112 (10)
V	113 (63)	125 (100)	112 (20)
VI	99 (100)	125 (45)	112 (12)
VII	99 (100)	125 (50)	112 (12)
VIII	157 (14)	125 (100)	112 (17)
IX	139 (10)	125 (100)	112 (20)
X	...	...	...
XI	99 (100)	139 (3.5)	...
XII	99 (100)	139 (4.5)	...
XIII	99 (100)	125 (41)	112 (9)
XIV	99 (100)	125 (4)	112 (9)
XV	99 (100)	125 (14)	112 (8)
XVI	...	125 (100)	112 (24)
XVII	99 (100)	...	...
XVIII	99 (100)	...	...
XIX	99 (100)	...	...
XX	99 (100)	...	...
XXI	99 (100)	...	...

The over-all effect is that 5α-androstan-3-one ethylene ketal (II) exhibits three characteristic fragmentations [(1), (2), and (3)], which are indicated schematically in representation IIa. If these fragmentations are to be of optimum structural utility, then it is important that the cleavage pattern be predominantly independent of further nuclear substitution which still permits the proposed mechanisms to operate. To investigate this point we have measured the mass spectra of a variety of differently substituted 3-ethylene ketals (III → XXI) and the data are summarized in Table I. The figures given in parentheses after each *m/e* value refer to the intensity of the ion relative to the base peak as 100.

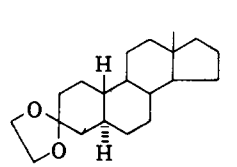
The results indicate that the ethylene ketal moiety strongly directs fragmentation in a consistent manner. In steroids which are monosubstituted at C-2 (V, VIII, IX), the ion formed by cleavage (1) shifts by an amount corrresponding to the mass increment associated with the substituent, while the ions from cleavages (2) and (3) are unmoved. Another important feature is that monosubstitution at C-2 increases the abundance of ruptures (2) and (3) relative to (1). The effect is larger (see Table I) in the presence of a C-2 carbomethoxy (VIII) or isopropenyl (IX) substituent than it is for a simple methyl group (V). This relationship is to be anticipated since initial fission of the 2–3 bond



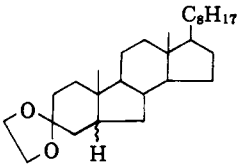
IIa, $R_1 = R_2 = H$
V, $R_1 = CH_3$, $R_2 = OH$
VI, $R_1 = H$, $R_2 = C_8H_{17}$
VII, $R_1 = H$, $R_2 = C_8H_{17}$ (5β-H)
VIII, $R_1 = COOCH_3$, $R_2 = C_8H_{17}$
IX, $R_1 = C(CH_3)=CH_2$, $R_2 = C_8H_{17}$
X, $R_1 = =C(CH_3)_2$ (no H at C-2), $R_2 = C_8H_{17}$



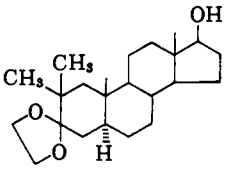
XI, R = C_8H_{17}
XII, R = OH



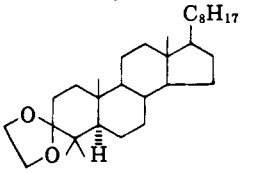
XIII



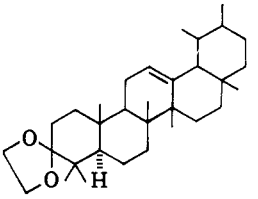
XIV, 5β–H
XV, 5α–H



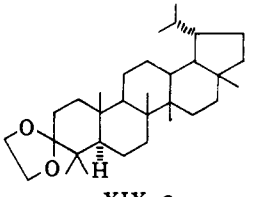
XVI



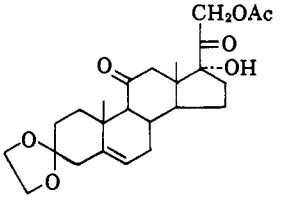
XVII



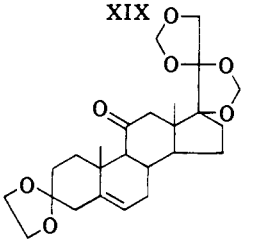
XVIII



XIX



XX



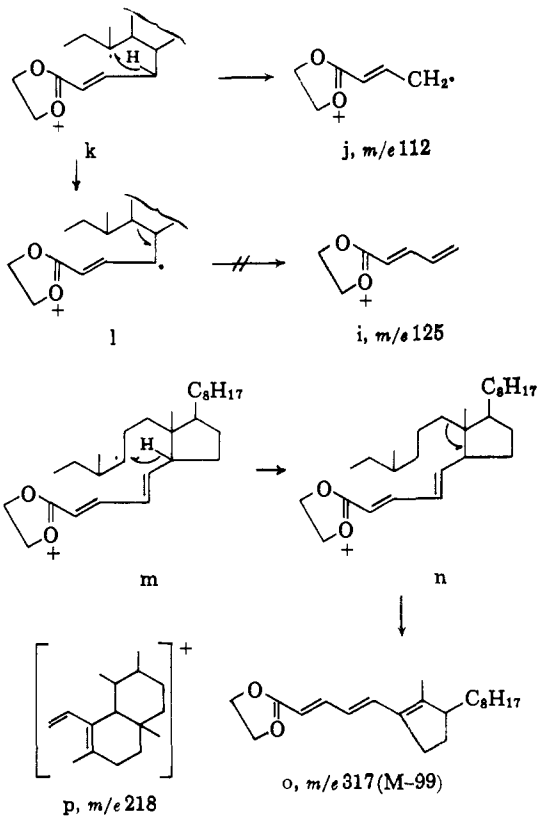
XXI

(II → e) will be most favored over the alternative 3–4 rupture (II → b) when radical character at C-2 is stabilized by an adjacent carbonyl group or double bond. The figures given for the isomeric cholestan-3-one and coprostan-3-one ethylene ketals (VI and VII, Table I) show that the cleavages are virtually independent of the stereochemistry at C-5. Similarly, the absence of a C-19 methyl group in the 19-nor ketal XIII causes no significant relative intensity changes for the three ions (*cf.* II and XIII, Table I). It is interesting to note that the introduction of a double bond at C-2 in the isopropylidine derivative X completely quenches all the characteristic modes of breakdown. This is to be expected since the step b → c in cleavage (1) is impossible in the absence of hydrogen at C-2, while for ruptures (2) and (3) the initial reaction (II → e) is inhibited by the unfavorable nature of a potential vinyl radical at C-2.

Monosubstitution at C-4 follows exactly the anticipated pattern. Thus the higher degree of substitution

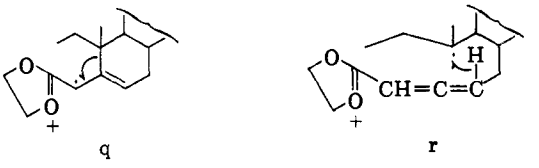
of C-4 now promotes process (1) over process (2) by approximately one order of magnitude. This can be seen on contrasting the data for the two 4α-methyl steroids XI and XII with those for the parent androstane ketal II (Table I). Furthermore, the product of rupture (2) shows the expected shift of 14 mass units, appearing at *m/e* 139. It is not surprising that the intensity of the peak derived from process (3) is sufficiently low in the spectra of XI and XII to cause it to disappear among other weak background ions of the scan. *Perhaps the most important point which is evident from the above discussion of monosubstitution is that it is now possible by means of mass spectrometry to determine the position of alkylation of a 3-ketone, irrespective of whether the parent compound is an A/B cis-, A/B trans-, or a 19-norsteroid.*

The ketal XIV of B-norcoprostan-3-one proved to be an interesting case. According to the mechanisms outlined earlier, we can arrive at an ion k, which is the B-nor analog of g and may furnish j (*m/e* 112). The ion k can also afford l, the B-nor equivalent of h, but l cannot give the *m/e* 125 species c. If one explores further possible decomposition paths for l, the usual type of bond homolyses and hydrogen transfers lead through the intermediates m and n to the production of an M − 99 species o (*m/e* 317). The spectrum (Fig. 2) of XIV fits the predictions beautifully. Cleavage (1) follows its usual course, giving rise to the base peak of the spectrum at *m/e* 99 (d). The intensity of the *m/e* 112 peak (j) is "normal," while the formation of an *m/e* 125 species i is almost completely quenched. Most gratifying is the presence of the medium intensity M − 99 peak (o), formed in a predictable and rational manner by no less than four C–C bond homolyses and three hydrogen transfer reactions in 10^{-6} sec. or less. (The elementary composition of the ion o was established by high resolution measurements using an MS-9 mass spectrometer.) The spectrum of XV, the 5α-epimer of XIV, follows exactly the same lines, except that the "forbidden" *m/e* 125 ion (i) becomes somewhat more intense (Table I), but only attains about 30% of its usual abundance.



We turn now to a consideration of disubstitution at C-2 and C-4. In the case of 2,2-dimethyl-5α-androstan-17β-ol-3-one ethylene ketal (XVI) we must expect cleavage (1) to be quenched in the absence of hydrogen at C-2 (see b → c), while fissions (2) and (3) will occur in the usual manner, just as is found (Table I). Conversely, in the 4,4-disubstituted steroid XVII and the ethylene ketals of the triterpenes α-amyrone (XVIII) and lupanone (XIX), the absence of hydrogen at C-4 inhibits processes (2) and (3) and in all three cases *m/e* 99 ions formed by cleavage (1) give by far the most intense peaks in the spectra. The retro-Diels–Alder reaction which is characteristic[13–15] of Δ^{12}-triterpenes can compete only slightly with the formation of *m/e* 99 ions and in the instance of XVIII gives rise to a peak at *m/e* 218 (p), which is 10% of the intensity of the base peak (*m/e* 99).

The data for the last two compounds in Table I, cortisone acetate ethylene ketal (XX) and the bismethylenedioxy derivative of cortisone ethylene ketal (XXI), are unexceptional, the allylic nature of the 3–4 and 1–10 bonds now strongly favoring cleavage (1). Hence *m/e* 99 is the base peak in both spectra, while the decomposition pathways (2) and (3) are not operative. One possible reason is that homolysis of the 5–10 linkage in q with resultant allene formation is unfavorable; alternatively transfer of a vinyl hydrogen in r seems equally unpalatable.



7-Ketals.—It will be apparent from the mechanism which has been outlined for cleavage (1), *i.e.*, II → b → c → d, that the apparent essential prerequisite for the formation of an abundant *m/e* 99 species d is a chain of two methylene groups adjacent to the ethylene ketal function. Therefore, it might be anticipated that if a monoethylene ketal is obtainable, steroids functionalized in rings B and C or at C-16, having only one methylene group adjacent to the functionality, could be readily differentiated from those oxygenated in ring A or at C-15 or C-17 since only the latter group should yield abundant *m/e* 99 ions. To investigate this hypothesis we have determined the spectra of a number of 7-ethylene ketals and these will now be discussed.[16]

In the mass spectrum (Fig. 3) of 5α-androstan-3β-ol-7-one ethylene ketal (XXII) the base peak occurs at *m/e* 141 (see also Table II) which corresponds exactly to cleavage (2) in 3-ethylene ketals and can therefore

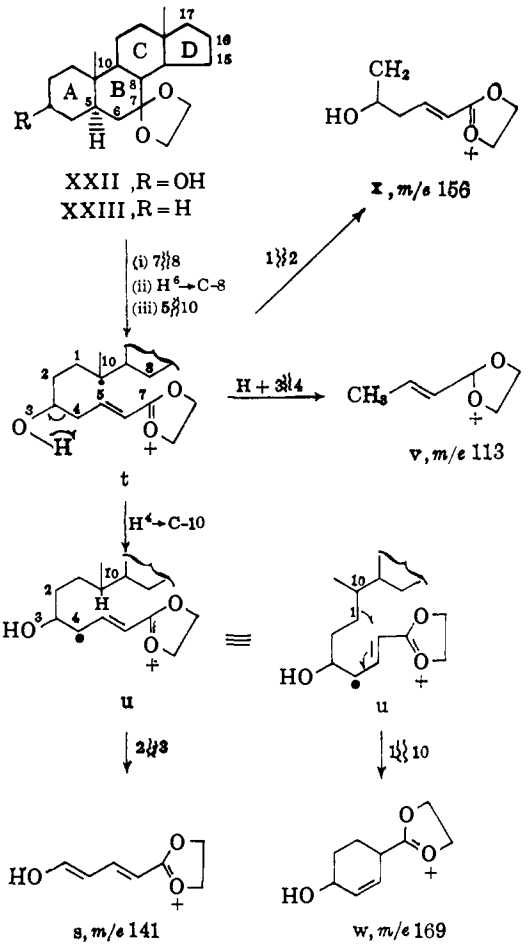
(13) C. Djerassi, H. Budzikiewicz, and J. M. Wilson, *Tetrahedron Letters*, 263 (1962).

(14) H. Budzikiewicz, J. M. Wilson, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 3688 (1963).

(15) J. S. Shannon, *Australian J. Chem.*, **16**, 683 (1963).

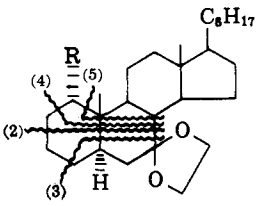
(16) While this work was in progress, a paper (ref. 5) dealing in part with the mass spectra of 7-ethylene ketals has appeared. We wish to thank Dr. M. Fétizon for a prepublication copy of this paper.

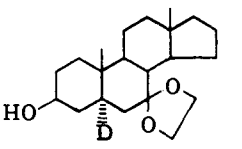
be attributed to s, arising *via* intermediates t and u. Fission (3) of 3-ethylene ketals could be expected also to give an *m/e* 112 species j in the present case, as is indeed observed in the absence of a hydroxyl group at C-3 [5α-androstan-7-one ethylene ketal (XXIII)[5]]. However, in Fig. 3, the most prominent ion in this region occurs at *m/e* 113, suggesting that the C-3 hydroxyl function participates in the final bond rupture as indicated by t → v. The partial transfer of the hydroxyl hydrogen to the charged species is in fact confirmed by deuterium labeling.

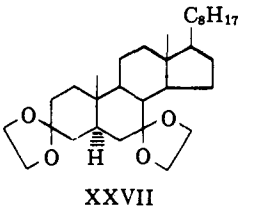


Alternatively, u can undergo homolysis of the 1–10 bond with concomitant formation of a six-membered ring to yield w (*m/e* 169), thus accounting for the ion of this *m/e* value in Fig. 3. A fourth prominent peak at *m/e* 156 in Fig. 3 may be accounted for by invoking homolysis of the 1–2 bond in t to afford x (*m/e* 156).

We will return later to a consideration of the *m/e* 99 and 230 ions of Fig. 3, but it is first appropriate to comment on the general nature of the above four cleavages. The total effect of the sequences outlined above is summarized in formula XXIV. Cleavages (2), (3), (4), and (5) can be correlated with the main peaks in the spectrum (Fig. 3) of XXII by reference to Table II. This table also gives the corresponding data for the 7-ethylene ketals XXIII → XXVII; the figures in parentheses after the *m/e* values again (see Table I) refer to the intensity of the ion relative to the base peak as 100.







It can be seen from Table II that the four fragment ions of the 3β-hydroxy-7-ketal XXII which are under discussion all show the anticipated shift of one mass unit in the spectrum of the 5β-d_1-analog XXVI. Cholestan-7-one ethylene ketal (XXIV) behaves consistently, cleavage (3) giving rise to an *m/e* 112 ion j rather than an *m/e* 113 species v in the absence of a hydroxyl group at C-3. It is also evident from Table II

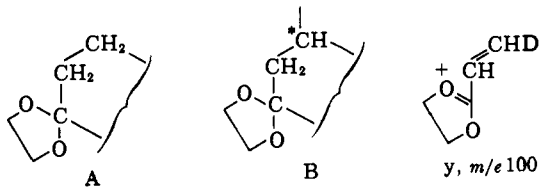
TABLE II

THE *m/e* VALUES OF IONS ARISING THROUGH CLEAVAGES (2), (3), (4), AND (5) IN 7-ETHYLENE KETALS (See XXIV)

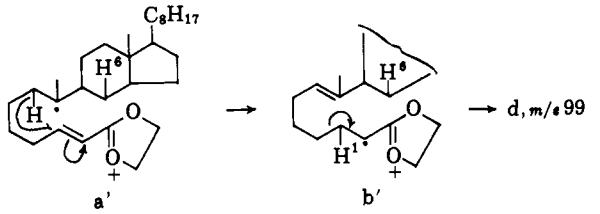
Compound	*m/e* values (2)	(3)	(4)	(5)
XXII	141 (100)	113 (24)	156 (30)	169 (14)
XXIII	125 (100)	112 (16)	...	153 (66)
XXIV	125 (100)	112 (21)	...	153 (52)
XXV	125 (100)	112 (20)	...	154 (56)
XXVI	142 (100)	114 (22)	157 (27)	170 (13)
XXVII	183 (100)	...	...	211 (3)

that cleavage (4) is only prominent in the presence of the same C-3 hydroxyl function. A most informative spectrum is that of 1α-d_1-cholestan-7-one ethylene ketal (XXV), in which only the ion formed by process (5) is shifted by one mass unit, thus providing strong support for the assignments. The introduction of two ethylene ketal functions into the same molecule does not appear to cause any complications. Hence, in the spectrum of cholestane-3,7-dione diethylene ketal (XXVII), ions appear due to the fissions characteristic of the 7-ketal moiety (see Table II), in addition to an abundant *m/e* 99 species (90% of the *m/e* 183 base peak) which can be attributed partly to rupture (1) as indicated in IIa.

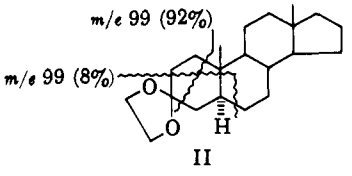
We now come to a consideration as to why the reservation "partly" must be added to the preceding sentence, for it was predicted that 7-ethylene ketals would be a class of compound which could not furnish an *m/e* 99 ion d. However, it is obvious from Fig. 3 that this prediction is not fulfilled, *m/e* 99 being 68% of the base peak intensity. A possible explanation of this phenomenon is that compounds such as 3-ethylene ketals, containing partial structure A, may furnish an *m/e* 99 ion by the sequence b → c → d indicated earlier, while 7-ethylene ketals incorporating the moiety B must first undergo hydrogen migration of C* before splitting off d.



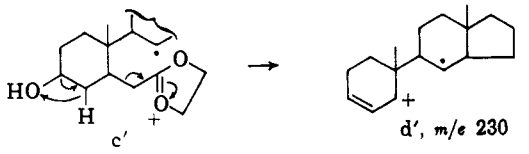
The fact that "forbidden" *m/e* 99 ions do find their origin in this manner was established by the spectrum of 5α-d_1-androstan-3β-ol-7-one ethylene ketal (XXVI), in which the *m/e* 99 ion was predominantly (80%) shifted to *m/e* 100 (y). Thus, it only remains to establish the origin of the hydrogen which migrates to C-5. Since a six-membered cyclic transition state seemed most probable, the 1α-d_1-ketal XXV was prepared and its spectrum determined. The observed partial shift of *m/e* 99 to 100 confirms that the sequence a′ → b′ → d operates to the extent of about 65% (calculated assuming no isotope effect) in the formation of the "forbidden" *m/e* 99 ion.



There is a course no reason why sequences analogous to a′ → b′ should not occur, even when the presence of the partial structure A permits the formation of *m/e* 99 ions by the simple b → c → d pathway. Indeed, close examination of the mass spectrum of 5α-d_1-androstan-3-one ethylene ketal (III) uncovers an 8% shift of the *m/e* 99 ion to 100 relative to the spectrum of the nondeuterated ketone II. Therefore, in the final analysis, the source of the *m/e* 99 ion of 5α-androstan-3-one ethylene ketal (II) is as indicated below. This finding emphasizes the unique advantage of deuterium labeling in mechanistic studies in mass spectrometry.



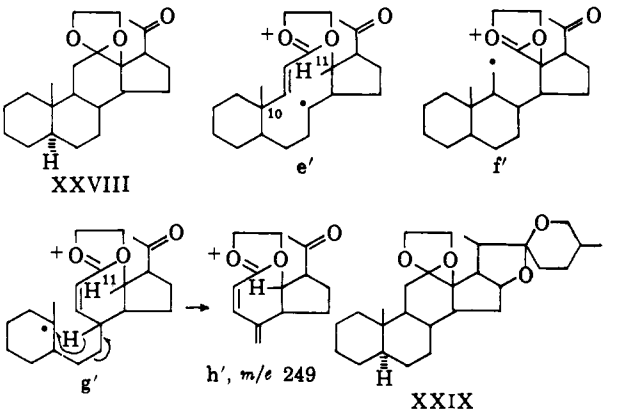
Finally, although the *m/e* 230 ion of Fig. 3 is not of great general importance, its mode of genesis deserves some comment. The ion arises from the loss of 104 mass units from the molecular ion (*m/e* 334), which can only reasonably correspond to M − $C_4H_8O_3$. Thus, both oxygen-containing substituents are lost in this fragmentation, a finding which is readily accommodated by expulsion of the ethylene ketal function with the attached C-6 methylene group and associated loss of water from the intermediate c′. These processes result in the formation of a favorable allylic carbonium ion d′ (*m/e* 230). The spectrum of the OD-derivative of XXII does in fact confirm that the C-3-hydroxyl group is expelled in this fragmentation.



Before leaving the topic of 7-ethylene ketals, it is worthwhile to emphasize the potentially great utility of cleavages (2)–(5) as represented in XXIV for the location of nuclear substituents in steroids suitably functionalized at C-7.

12- and 16-Ketals.—Our results for 17- and 20-ethylene ketals have been reported[3,4] previously and require no further comment here. Although ethylene ketal derivatives of highly hindered 11-ketones have not yet been prepared, those of 12- and 16-ketones are fairly readily available and have been studied.[17] The results indicate that despite the complications of *m/e* 99 fragment ions being formed by multiple rearrangement processes (probably analogous to those outlined for 7-ethylene ketals), the presence of other ions characteristic of C-12 or C-16 functionalization may prove helpful in detecting this type of nuclear oxygenation.

Relatively little fragmentation occurs in the spectrum (Fig. 4) of 5α-pregnane-12,20-dione 12-ethylene ketal (XXVIII), the molecular ion being the base peak. A consideration of the established decomposition modes of ethylene ketals upon electron impact clarifies this behavior, since in 12-ketals, the characteristic cleavages are mostly blocked by the lack of suitable hydrogen atoms to participate in the rearrangement processes. Thus, the absence of hydrogen atoms at C-10 and C-13 in the decomposition intermediates e′ and f′, respectively, renders their further fragmentation in the usual manner impossible. However, in the case of g′, complete scission of the molecule is eventually possible yielding h′ (*m/e* 249), which is an observed, though admittedly small, peak in Fig. 4. The main features of the high mass range of the spectrum (Fig. 4) appear at *m/e* 317 (M − 43), 298 (M − 62), and 255 (M − 105), presumably corresponding to the loss of the C-17 side chain (M − $COCH_3$), ethylene glycol (M − $C_2H_4(OH)_2$), and these two moieties combined, respectively. As expected, a prominent peak is evident at *m/e* 99 (d).



In the spectrum of 3-deoxyhecogenin ethylene ketal (XXIX), the molecule ion is again the base peak.

(17) The mass spectrum of cholestan-6-one ethylene ketal has been reported in ref. 5.

TABLE III

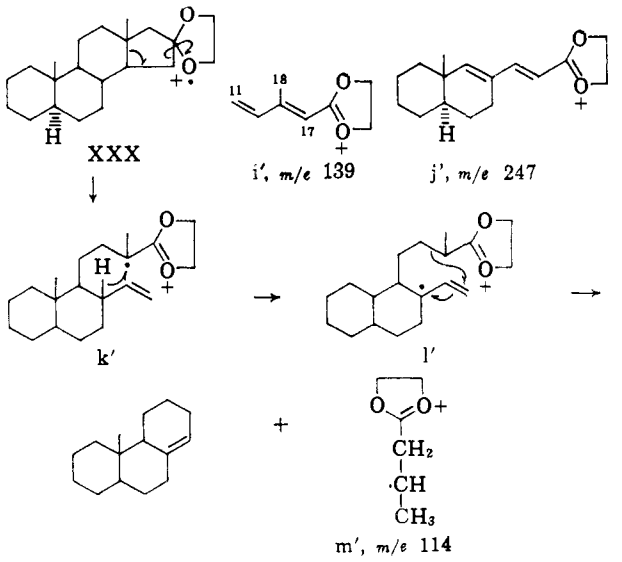
PHYSICAL CONSTANTS OF ETHYLENE KETALS

Compound	M.p., °C.	Microanalyses, % Calcd. C	Calcd. H	Found C	Found H	[α]D (c, CHCl3)
XI ($C_{30}H_{52}O_2$)	118.5–119.5	81.02	11.79	80.87	11.56	+14.6° (1.0)
XII	205.5–206					+5.6 (0.9)
XVII ($C_{31}H_{52}O_2$)	154–155.5	81.16	11.82	81.09	11.56	−5.1 (1.0)
XVIII ($C_{32}H_{52}O_2$)	198.5–201	81.99	11.18	81.83	11.08	
XIX ($C_{32}H_{54}O_2$)	199–200	81.64	11.56	81.63	11.28	+41.1 (0.36)
XXVIII	179–180	76.62	10.06	76.57	9.97	+124.3 (1.0)
II	116–117 (lit.[18] 116–117)					
VI	115.5–116 (lit.[19] 111–113)					

Compound	M.p., °C.
VII	53–54 (lit.[19] 51–52)
XIII	94.5–95.5
XIV	41–43
XV	81–83
XVI	190–192
XXII	177–178
XXVII	218–219
XXIX	165–167

The fragmentation occurring gives rise to an abundant *m/e* 99 ion, most of the remaining decomposition modes being characteristic of the sapogenin side chain.[20] It is not surprising that the spiroketal system of the sapogenin side chain, in itself closely analogous to an ethylene ketal moiety, triggers sufficient fragmentation to render the formation of the characteristic ion exemplified by h′ almost negligible.

The mass spectrum of 5α-androstan-16-one ethylene ketal (XXX) is reproduced in Fig. 5 and follows the expected pattern. Thus the cleavages indicated in the figure give rise to ions i′ (*m/e* 139) and j′ (*m/e* 247), respectively. The ion *m/e* 99 (d) is, as usual, also in evidence, the only unexpected feature being an abundant fragment at *m/e* 114. This unique feature, although *a priori* unpredictable, may be attributed to the sequence k′ → l′ → m′ (*m/e* 114).



Conclusions

In summary, it can be said that although insufficient spectra have been determined so far to permit wider generalizations, the specific manner in which the ethylene ketal function directs fragmentation should greatly facilitate functional group and substituent location. Many 3-ketals have been examined and as a result it can be stated that one can readily differentiate between mono- and disubstitution at C-2 or C-4. It may be anticipated that cleavages characteristic of an ethylene ketal in any position will be completely blocked when quaternary carbon atoms are created at sites which normally supply migratory hydrogen atoms.

In general, the appearance of an *m/e* 99 ion several times more intense than any of the ions in the spectrum is indicative of a sequence of two methylene groups adjacent to the functionality. Alternatively, if the *m/e* 99 ion is of the same order of magnitude as several other ions in the spectrum, it has probably been formed by a rearrangement process of the type shown to operate in cholestan-7-one ethylene ketal (XXIV).

Experimental[21]

General Procedure for the Preparation of Ethylene Ketals.—The ketone (0.2 g.) and *p*-toluenesulfonic acid (0.1 g.) in toluene (60 ml.) and ethylene glycol (20 ml.) were heated at reflux temperature with continuous slow removal of the solvents by distillation. The reaction was followed by thin layer chromatography. Upon completion of the reaction (~7 hr.), pyridine (2 ml.) was added to the mixture. The organic phase was washed with water, dried, and evaporated under vacuum, and the residue crystallized from acetone–methanol, containing 1 drop of pyridine. The yields were practically quantitative in all cases.

Physical Constants of Ethylene Ketals.—All ketals were characterized by melting point and the mass spectrometrically determined molecular weight. In those cases where microanalyses and optical rotations are available, they are given in Table III.

The 5α-d_1- and 7β-d_1-derivatives of 5α-androstan-3-one ethylene ketal (II) (compounds III and IV) were prepared by ketalization of 5α-d_1-androstan-3-one[11] and 7β-d_1-androstan-3-one,[22] respectively, while the parameters of 2α-methoxycarbonylcholestan-3-one ethylene ketal (VIII) and 2α-isopropenylcholestan-3-one ethylene ketal (IX) have been described previously.[23] Ketalization of 5α-d_1-androstan-3β-ol-7-one[11] afforded XXVI, identical

(18) A. Marquet, M. Dvolaitsky, H. B. Kagan, L. Mamlok, C. Ouannes, and J. Jaques, *Bull. soc. chim. France*, 1822 (1961).

(19) H. J. Dauben, B. Loken, and H. J. Ringold, *J. Am. Chem. Soc.*, **76**, 1359 (1954).

(20) H. Budzikiewicz, J. M. Wilson, and C. Djerassi, *Monatsh.*, **93**, 1033 (1962).

(21) Melting points are corrected and were determined on a Kofler block. Rotations were measured in chloroform, while thin-layer chromatography was performed on silica gel G (E. Merck, A.G., Darmstadt), the spots being developed by spraying with a 2% solution of ceric sulfate in 2 *N* sulfuric acid and subsequent heating. Mass spectra were determined with a Consolidated Electrodynamics Corp. mass spectrometer No. 21-103C using an all-glass inlet system heated to 200°, while the isatron temperature was maintained at 270°. The ionizing energy was kept at 70 e.v. and ionizing current at 50 μa. All microanalyses were carried out by Messrs. E. Meier and J. Consul.

(22) G. von Mutzenbecher, unpublished results.

(23) C. Djerassi, P. A. Hart, and C. Beard, *J. Am. Chem. Soc.*, **86**, 85 (1964).

in melting point with the nondeuterated analog XXII described in Table III.

2α-Bromocholestan-7β-ol-3-one[24] was converted into 1α-d_1-cholestan-7β-ol-3-one by standard chemical procedures.[25]

1α-d_1-Cholestan-7-one Ethylene Ketal (XXV).—1α-d_1-Cholestan-7β-ol-3-one (145 mg.) in triethylene glycol (4 ml.), *n*-butyl alcohol (1.5 ml.), and 95% anhydrous hydrazine (1 ml.) was heated under reflux for 2 hr. After cooling the mixture, potassium hydroxide (0.5 g.) was added. Solvent was then removed by distillation until the temperature of the solution reached 200°. Heating was continued for 4 hr. at 200–210°, after which time the organic material was isolated in the conventional manner. The crude product (121 mg.) in acetone (3 cc.) was treated with a slight excess (10%) of 8 *N* chromic acid solution.[26] This solution was diluted with water and ether, and the ether phase washed twice with water, dried, and evaporated. The residue (110 mg.) so obtained was crystallized from methanol affording 1α-d_1-cholestan-7-one (75 mg.), m.p. 117–118°. This material was converted to 1α-d_1-cholestan-7-one ethylene ketal (XXV), m.p. 122–123°, by the standard method outlined above. The unlabeled ethylene ketal XXIV derived directly from cholestan-7-one had an identical melting point.

(24) We wish to thank Dr. T. Nakano (University of Kyoto) for a generous gift of this material. We are also indebted to Syntex S.A., Mexico City, for samples of compounds V and XIII and to Dr. S. Bernstein and L. H. Sarett for samples of the cortisone derivatives XX and XXI.

(25) See, for example, D. H. Williams, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2091 (1963).

(26) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STEVENS INSTITUTE OF TECHNOLOGY, HOBOKEN, N. J.]

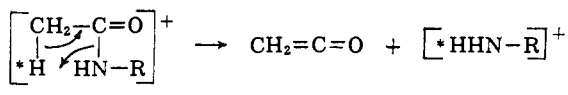
Mass Spectral Studies. III. Fragmentation of Aromatic Amides[1]

BY K. G. DAS, PHILLIP T. FUNKE, AND AJAY K. BOSE

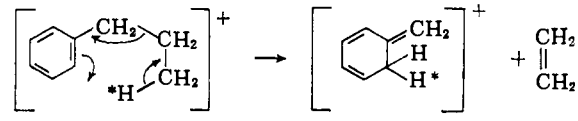
RECEIVED MARCH 18, 1964

A study of the mass spectra of several aromatic amides, their deuterated forms, and analogs has been made. The major fragmentation in N,N-diphenylphenylacetamide (Ia) and analogs involves the transfer of a proton from the acyl group to the nitrogen. In diphenylacetanilide (IIa) and analogs the base peak is formed by the transfer of a proton from the nitrogen to the acyl group. Deuteration studies and direct comparison with the spectra of diphenylamine and diphenylmethane indicate that a four-membered ring transition state is favored over a six-membered one. Carbazole and fluorene seem to be possible intermediates in the stepwise fragmentation of Ia and IIa. A simple cleavage of the type (>C–C(=O)–N–) was observed in aromatic amides when stable carbonium ions are formed as a result of this cleavage. A new type of rearrangement involving the migration of an aryl group from nitrogen to the carbon atom α to the carbonyl group was noticed in the spectrum of N,N-diphenylphenylacetamide (Ia) and its analogs. Dideuteration was observed to reduce markedly the aryl migration caused by deuterium isotope effect. No migration of an aryl group from carbon to nitrogen was observed in the spectrum of diphenylacetanilide (IIa) and its analogs.

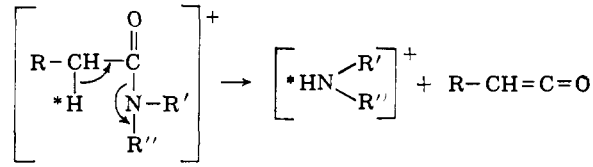
The mass spectral fragmentation patterns for a variety of aliphatic amides have been discussed recently.[2] Lately it has been shown[3] by deuteration studies that one of the major fragmentation modes in aliphatic amides is the transfer[4] of a proton from the acyl group to the amino nitrogen. We present here our findings on aromatic amides.



N,N-Diphenylphenylacetamide and Its Analogs (Fig. 1 and 2).—As expected from the analogy with aliphatic amides, we observed the fragments formed by the scission of the amide bond and from the transfer of a proton from the acyl group to the amine fragment. The latter fragment gave the base peak in the spectra of N,N-diphenylphenylacetamide, its deuterated form,[4] and analogs (such as Ib and Ic). The metastable peak at *m/e* 100.5 supports this rearrangement (calcd. 100.2 for *m/e* 298 → *m/e* 169). In aliphatic amides this proton transfer can take place only through a four-membered ring transition state as shown by Djerassi.[3] But McLafferty[5] has shown, also by deuteration studies, that a six-membered ring transition state and the transfer of a proton to the phenyl group are involved in rearrangements of the type



We can write a four-membered ring transition state and/or a six-membered ring transition state to explain the proton transfer in the amide Ia.



Ia, R = R′ = R″ = C_6H_5 (metastable peak at 100.5; calcd. 100.2 for *m/e* 287 → 169)

b, R = *p*-tolyl, R′ = R″ = C_6H_5 (metastable peak at 95.5; calcd. 94.9 for *m/e* 301 → 169)

c, R = C_6H_5, R′ = R″ = *p*-tolyl (metastable peak at 124; calcd. 123.2 for *m/e* 315 → 197)

(1) Part II: P. Funke, K. G. Das, and A. K. Bose, *J. Am. Chem. Soc.*, **86**, 2527 (1964).

(2) J. A. Gilpin, *Anal. Chem.*, **31**, 935 (1959); see also F. W. McLafferty, *ibid.*, **28**, 306 (1956).

(3) Z. Pelah, M. A. Kielczewski, J. M. Wilson, M. Ohashi, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2470 (1963).

(4) Protons exchangeable with deuterium are marked with an asterisk.

(5) F. W. McLafferty, "Mass Spectrometry of Organic Ions," Academic Press, Inc., New York, N. Y., 1963, p. 337; see also K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 122–124.