

Mass Spectra of 6-Ketononanolides and Related Ketolactones

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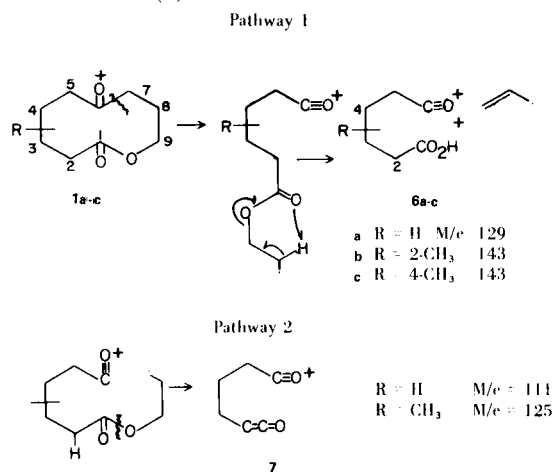
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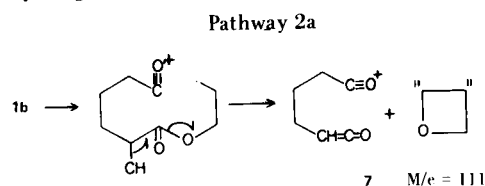
The mass spectral fragmentation of 6-ketononanolides, 6- and 7-ketodecanolides, 7-ketoundecanolides and 9-ketotridecanolide has been partially correlated *via* high resolution measurements and the use of methyl substituted derivatives. Moieties characteristic of the "lactone side" and the "non-lactone side" of the ketolactones can be described. Metastable transitions and decoupled measurements are offered as additional evidence for some of these pathways.

We wish to report a study on mass spectral fragmentation pathways found in the 6-ketononanolide (**1a-f**), 6-ketodecanolide (**2**), 7-ketoundecanolide (**3a-c**), 9-ketotridecanolide (**5**), and 2,4,6-trimethyl-7-ketodecanolide (**4**) systems. Compounds **3a** and **5** represent simplified versions of the methymycin and erythromycin macrolide antibiotics. Several mass spectral studies on erythromycin and related macrolides have recently appeared (1,2).

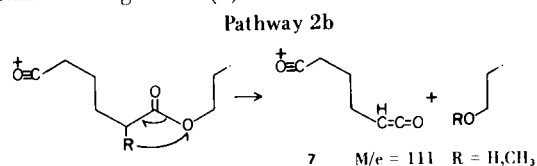
The high-resolution electron-impact mass spectra of 6-ketononanolide (**1a**) and several of its methyl-substituted derivatives (**3**) can be rationalized on the basis of several fragmentation pathways. These pathways are formulated partially by using a methyl group as a substituent label. Such studies are valid if the substituent does not alter the fundamental fragmentation mechanisms but merely results in the appropriate mass shifts for fragments bearing the substituent. Pathways 1 and 2 give fragments that contain carbons 1-6, the "non-lactone side" of the ring. Relevant data utilizing exact elemental compositions is given in Table I (4).



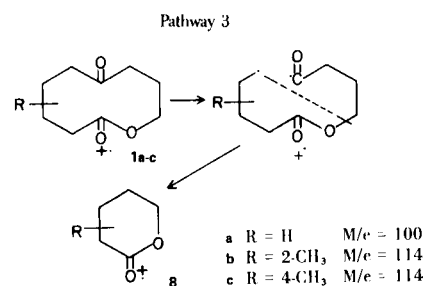
2-Methyl-6-ketononanolide (**1b**) does not properly correlate, *i.e.* the anticipated enhancement of M/e 125 *vs.* 111 and 143 *vs.* 129 is not found (while these enhancements are found in **1c**). This may be due to loss of the methyl group, which is α to the lactone carbonyl, in competition with hydrogen loss.



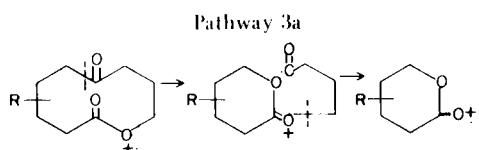
Alternatively, **1b** may undergo a 4-center thermal cyclic process as may occur in macrolide mass spectra (5). The latter spectra are too complex to ensure the validity of of this rearrangement (5).



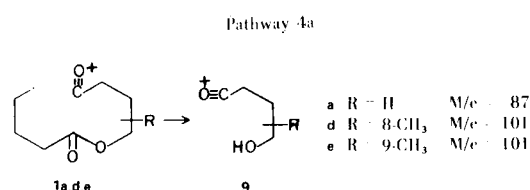
Pathway 3 gives a fragment containing carbons 1-5, possibly the "lactone" structure illustrated (see data in Table I, pathway 3).



An alternate pathway (3a) which does not require two discrete breaks can also be envisaged (5).

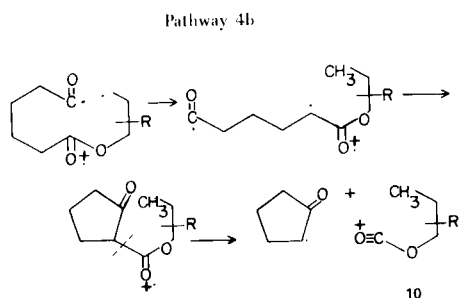


A predominant fragmentation (pathway 4a) involves α -cleavage and formation of a hydroxyalkyl carbonyl fragment containing carbons 6-9 of the "lactone side".



The suggestion that the fragment of M/e 87 contains the ketone carbonyl is based on its loss of water to give M/e 69 as evidenced by a metastable transition at 54.7 for this process (Table IV), and the prominence of M/e 69 (6.3%) in the mass spectrum of **1a**. It is recognized that other pathways to M/e 69 fragments can exist in the mass spectra of ketones (6).

The M/e 87 fragment also contains the lactone carbonyl, as in **10**. This fragment could arise as shown in pathway 4b. Evidence for **10** includes a metastable peak at 21.2 for the loss of carbon dioxide (87 \rightarrow 43, Table IV) and a weak peak at 43 (1.5%). Metastable decoupling data (Table IV) further strengthen paths 4a and 4b.

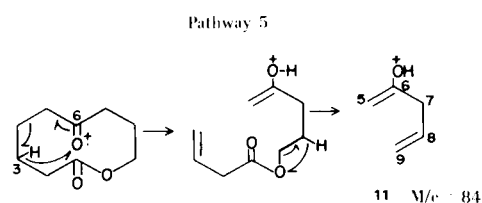


These pathways (4a, 4b) become even more important for the 11-14 membered ring ketolactones (see below).

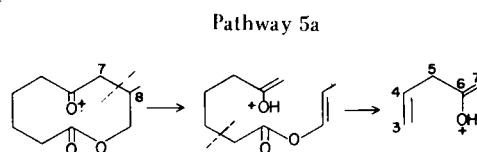
Related pathways are found in the mass spectral fragmentation of macrolides (5). The mass spectra of the 9-methyl ketolactone **1e** and 7-keto-8,11-dimethylundecanolide (**3c**, pathway 4, Tables I, II), which have methyl groups next to lactone oxygen and are thus related to the macrolides which have alkyl groups in that position, show peaks at 101 and 129, respectively. These peaks correspond to the M/e 87 fragment in **1a**. Peaks corresponding to the loss of water from these moieties at 83 and 111 are also found, suggesting pathway 4a. A metastable at 68.2 for the 101 to 83 transition in **1e** is found. Evidence for

pathway 4b for **1e** and **3c** is not found.

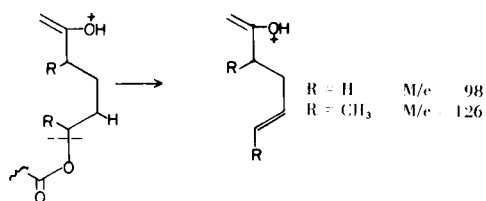
The most prominent peak in the high resolution mass spectrum of **1a** is for C₅H₈O, M/e 84. On the basis of the relative intensities of 84, 98 and 112 for the series **1a-f** (Table I, pathway 5) much of the **84** fragment involves carbons 5-9. It may arise *via* an intramolecular McLafferty rearrangement (pathway 5).



Inspection of Dreiding models of **1a** shows that a C-3 hydrogen can approach the carbonyl oxygen to within a 1.2 Å distance, well within the 1.8 Å limit for McLafferty hydrogen transfer (7). The alternative of lactone opening before McLafferty rearrangement, is also possible and may be preferable (5). The unexpectedly low intensity for M/e 98 in the 8-methyl lactone (**1d**), as well as the relatively large intensities for 98 in the 2- and 4-methyl lactones (**1b**, **1c**, where 98 should be much less intense than is 84) suggest that there must also be other origins for M/e 84 involving carbons 2-6 or 3-7. The α -cleavage which would initiate the latter fragmentation may be enhanced by the 8-methyl group, thus explaining the positive ratio of M/e 84/98 in **1d**.

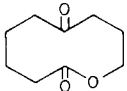
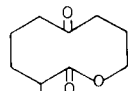
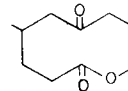
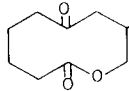
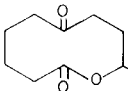
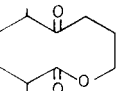


The larger ketolactones: 6-ketodecanolide (**2**, **8a**) the 7-ketoundecanolides **3a-3c** (**8a**, **b**), 9-ketotridecanolide (**5**, **8c**) and 2,4,6-trimethyl-7-ketodecanolide (**4**, **3**, **8a**) are similarly correlated in Table II. Paths 1-4 correlate well with the exception of **3b** in pathway 3 wherein α -methyl loss may be a factor (although such loss is not found in pathway 2). The predominant peak at M/e 98 for **2**, **3a**, **3b**, **5** and at M/e 126 for **3c** (pathway 5) is presumably formed in a similar manner to the M/e 84 peak for the 6-ketoneanolides.



The well known loss of groups next to lactone ring oxygen (9) is found for 8-methyl-6-ketoneanolide (**1e**)

Table I
Fragmentation Ions (Relative Intensities) (a)

						
Pathway 1 1a → 6	1a	1b	1c	1d	1e (b)	1f
M/e						
129 C ₆ H ₉ O ₃	0.9	1.07	0.10	8.45	11.9	
143 C ₇ H ₁₁ O ₃	--	0.42 (c)	1.17	--	--	
157 C ₈ H ₁₃ O ₃	--	--	--	--	0.2	
Pathway 2 1a → 7	1a	1b	1c	1d	1e (b)	1f
M/e						
111 C ₆ H ₇ O ₂	8.35	4.59	1.87	15.03	3.48	
125 C ₇ H ₉ O ₂	--	1.6 (b)	10.33	1.19	0.44	
139 C ₈ H ₁₁ O ₂	--	--	0.09	--	--	
Pathway 3 1a → 8	1b	1b	1c	1d	1e (b)	1f (b)
M/e						
100 C ₅ H ₈ O ₂	9.50	1.48	3.77	4.28	33.6	1.2
114 C ₆ H ₁₀ O ₂	--	6.59	7.99	0.35	0.3	1.2
128 C ₇ H ₁₂ O ₂	--	1.30	--	--	0.3	2.5
Pathway 4 1a → 9 (or 10)	1a	1b	1c	1d	1e (b)	1f (b)
M/e						
87 C ₄ H ₇ O ₂	19.28	20.86	25.99	0.22	--	7.4
101 C ₅ H ₉ O ₂	2.99	6.67	2.07	25.63	1.9	0.6
115 C ₆ H ₁₁ O ₂	0.08	6.71	5.16	--	--	--
Pathway 5 1a → M/e 84	1a	1b	1c	1d	1e (b)	1f (b)
M/e						
84 C ₅ H ₈ O	100.0	100.0	100.0	55.29	31.5	20.4
98 C ₆ H ₁₀ O	0.91	73.07	29.61	32.69	28.6	27.4
112 C ₇ H ₁₂ O	0.67	2.32	--	--	0.8	21.2

(a) Percentage of ionization values are in similar proportion. (b) Low resolution mass spectral data. (c) Value too low. See discussion.

and 8,11-dimethyl-7-ketododecanolide (**3c**) which show M-CH₃ peaks at 169 and 211, respectively.

The relative importance of hydrocarbon fragments increases with increasing ring size and molecular weight in cycloalkanones (10). A comparison of several oxygen-containing fragmentations for the 10-, 12- and 14-membered ketolactones (**1a**, **3a**, **5**) shows a reasonably constant percentage of ionization (Table III) so that the correlations noted above would seem to be about equally important throughout the series.

In addition to other similarities already mentioned, the

mass spectra of the macrolides show fragmentation related to pathways 1 and 2 for our ketolactones. Thus Erythronolide B gives the fragment ions **12** and **13** (1).

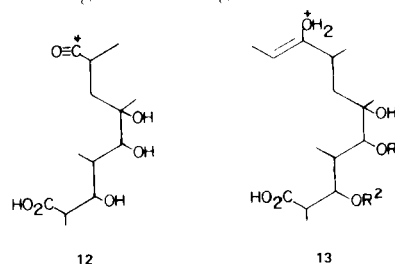
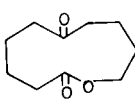
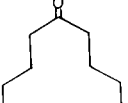
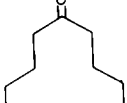
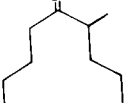
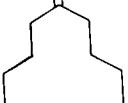
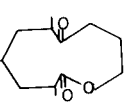


Table II

Fragmentation Ions (Relative Intensities)

						
Pathway 1	2	3a	3b	3c	5	4
M/e						
129 C ₆ H ₉ O ₃	17.69	--	--	--	--	--
143 C ₇ H ₁₁ O ₃	--	3.79	--	24.63	--	--
157 C ₈ H ₁₃ O ₃	--	--	1.93	--	--	--
171 C ₉ H ₁₅ O ₃	--	--	--	--	4.95	--
Pathway 2						
111 C ₆ H ₇ O ₂	15.03	--	--	--	--	--
125 C ₇ H ₉ O ₂	0.59	6.51	0.97	15.35	--	--
139 C ₈ H ₁₁ O ₂	0.18	--	2.12	--	--	--
153 C ₉ H ₁₃ O ₂	--	--	--	--	4.21	--
Pathway 3						
M/e	2	3a	3b	3c	5	4(a)
100 C ₅ H ₈ O ₂	13.80	1.40	1.69	--	--	--
114 C ₆ H ₁₀ O ₂	2.07	3.07	2.95	7.62	1.50	--
128 C ₇ H ₁₂ O ₂	0.68	0.18	1.54	0.41	--	--
142 C ₈ H ₁₄ O ₂	--	--	--	--	--	0.2
156	--	--	--	--	--	0.6
Pathway 4						
87 C ₄ H ₇ O ₂	--	--	--	--	--	15.0
101 C ₅ H ₉ O ₂	100.00	46.52	33.31	--	36.05	0.6
115 C ₆ H ₁₁ O ₂	1.57	3.57	4.69	--	--	2.7
129 C ₇ H ₁₃ O ₂	--	--	--	21.87	--	--
Pathway 5						
98 C ₆ H ₁₀ O	74.05	100.00	100.00	10.87	100.00	100.0
112 C ₇ H ₁₂ O	0.68	3.22	40.6	--	--	16.0
126 C ₈ H ₁₄ O	--	--	--	27.39	--	--

(a) Low resolution mass spectral data only

In partial confirmation of the postulated mass spectral pathways, metastable peaks and metastable decoupled measurements of m_d/m_p (the mass ratio of daughter to parent ions for metastable transitions) were measured and are recorded in Table IV. The only pathway for which a metastable peak is found directly is pathway 5. Evidence for the structure of the postulated ions **6**, **8**, **9**, and **10** (involved in pathways 1, 2, 3, 4a and 4b, respectively) is found *via* metastable peaks for the further decomposition of these ions involving loss of carbon dioxide or water.

The direct measurement of m_d/m_p by the variable

electric sector method confirmed the postulated origin of some of the observed metastable peaks. In addition, some weak transitions were thus observed for which the calculated metastable peak could not be observed. Notably, this group included the transition for the conversion of **1a** to M/e 100 (pathway 3).

EXPERIMENTAL

High resolution mass spectra were obtained on all compounds except **1e**, **1f**, and **4** with an AEI MS-9 mass spectrometer using the direct insertion probe, an ionizing potential of 70 eV, and a

Table III

The Relative Importance of Certain Fragmentations with Ring Size

Fragment (a)	M/e	1a		M/e	3a		M/e	5	
		Rel. %	Inten.		Rel. %	Inten.		Rel. %	Inten.
M ⁺	170	10.6	2.7	198	5.54	1.0	226	3.43	0.7
CH ₂ =C- ⁺ OH									
(CH ₂) _n CH=CH ₂	84	100.0	25.8	98	100.00	18.0	98	100.00	20.1
CH ₂ =CH-C≡ ⁺ O	55	69.5	17.9	55	50.7	9.1	55	25.5	5.1
⁺ O≡C-(CH ₂) _x OH	87	19.3	5.0	101	46.5	8.4	101	36.1	7.3
C≡ ⁺ O									
(CH ₂) _y -CH=C=O	111	8.4	2.2	125	6.5	1.2	153	4.2	0.9

(a) n = 1, 2; x = 3, 4; y = 3, 4, 6. (b) Based on intensity summation from M/e 43 to parent peak.

Table IV

Metastable Transitions in the Mass Spectrum of 1a

Obsvd	Metastable Peak		Origin of Metastable (a)		Postulated Pathway
	Calcd M/e		Mother Ion	Daughter Ion	
21.2	21.5		87 (b)	43 (b)	10 - CO ₂ ; related to path 4b
28.0 (c)	28.0		170	69	may be related to path 4a
31.3	31.3		100 (b, c)	56 (b, c)	8 - CO ₂ , related to path 3
41.5	41.5		170 (b)	84 (b)	path 5
54.7	54.7		87 (b, c)	69 (b, c)	9 - H ₂ O, related to path 4a
	58.8		170 (b, c)	100 (b, c)	M ⁺ → 8, path 3
67.6	67.6		142	98	(M-CO) - CO ₂
72.5 (c)	72.5		170 (b)	111 (b)	M ⁺ → 7, path 2
95.5	95.5		129	111	6 - H ₂ O, related to paths 1, 2
118.6	118.6		170	142	M ⁺ - CO
135.9	135.9		170 (b)	152 (b)	M ⁺ - H ₂ O

(a) Postulated values unless measured directly as indicated. (b) Directly measured as m_d/m_p by metastable decoupling *via* the electric sector method on a DuPont CEC 21-492 spectrometer. (c) Small peak or weak transition.

source temperature of about 200°. The measured masses of most of the ion peaks discussed were well within 10 ppm of the calculated masses (11).

Single-focused mass spectra for 1e, 1f, and 4 were obtained on a modified CEC 21-103C mass spectrometer utilizing a "Mascot" mass spectrum digitizer which had been previously calibrated for mass readout with internal standards. The samples were injected as solids utilizing a Micro-Tek high temperature inlet system (12).

The synthesis of the ketolactones other than 3c has been previously described (3, 8).

Metastable decoupling measurements were performed on a DuPont CEC 21-492 mass spectrometer. The metastable peaks for 1a were visually determined from a single-focused mass spectrum done on a Hitachi RMU-6 spectrometer at Columbia University (13).

7-Keto-8,11-dimethylundecanolide (3c).

Reaction of 2,5-dimethyltetrahydrofuran with acetyl bromide

and zinc chloride at 0°, as for tetrahydrofuran (8a), gave 2-bromo-5-acetoxyhexane (14, 69-83%); b.p. 121° (50 mm); vpc (5% SE-30, 125°) 1 peak 2.5 minutes; nmr (carbon tetrachloride); δ 1.2 (d, 3, C₅-CH₃), 1.6-1.9 (s, 4, C₃-H, C₄-H), 1.72 (d, 3, C₃-CH₃), 1.95 (s, 3, C₅-OCOCH₃), 4.0 (m, 1, C₅-H), 4.8 (m, 1, C₂-H).

Addition of 2-carbethoxycycloheptanone in toluene-DMF (4:1) to a suspension of sodium hydride (1.1 equivalent) in hexane-toluene under nitrogen, was followed by a reflux period of 30 minutes and then further addition of sodium hydride (0.5 equivalent) and further heating at reflux for 30 minutes. Dropwise addition of 14 (1.1 equivalent) was followed by a reflux period of 45 minutes. The resultant mixture was cooled, concentrated to 0.5 its volume, acidified with acetic acid, filtered, evaporated *in vacuo*, and distilled to give 2-carbethoxy-2-(2'-acetoxy-5'-methylpentyl)cycloheptanone (15, 51%); b.p. 140-147° (0.2 mm); vpc (5% SE-30, 170°) 1 peak 2.5 minutes; ir (film): 1730, 1700 cm⁻¹; nmr (carbon tetrachloride): δ 1.47

(m, 1, C₄-H), 0.8-1.95 (m, 25, alicyclic, C-CH₃), 1.95 (s, 3, COCH₃), 2.4 (m, 2, C₇-H), 4.1 (2q, 2, COCH₂CH₃). No O-alkylation was noted by this spectral data.

Anal. Calcd. for C₁₈H₃₀O₅: C, 66.23; H, 9.26. Found: C, 66.37; H, 9.42.

Hydrolysis of **15** with sodium hydroxide in 95% ethanol gave **2**(2'-hydroxy-5-methylpentyl)cycloheptanone (**16**, 45%); b.p. 120-125° (1.5 mm); vpc (5% SE-30, 135°) major peak *ca.* 3 minutes and minor peaks. Redistillation gave pure **16**; b.p. 126-128° (0.15 mm); one peak by vpc; nmr (carbon tetrachloride): δ 0.87 (d, 3, C₅-CH₃), 1.15 (d, 3, C₂'-CH₃), 1.1-2.0 (m, 13, ring H, C₃'-4'-5'-H), 2.0 (d, 1, C₂-H), 2.3 (m, 2, C₇-H) 2.55 (s, 1, OH), 3.6 (m, 1, C₂-H).

Anal. Calcd. for C₁₃H₂₄O₂: C, 73.54; H, 11.39. Found: C, 73.66; H, 11.22.

Slow distillation of **16** from potassium pyrosulfate (10% by weight) *in vacuo* (24 hours) gave 3,6-dimethyl-2-oxabicyclo-[5.5.0]dodec-1(7)ene (**17**, 73%), collected at -50°; b.p. 80-100° (0.08 mm); ir (film): 1660 cm⁻¹, no OH nor C=O. Oxidation of **17** with excess m-CPBA (3 equivalents) as for other bicyclic enol ethers (8) gave crude *cis*, *trans*-7-keto-8,11-dimethylundecanolate (**3c**) as a low melting solid. Recrystallization from petroleum ether at -5°, chromatography on silica gel (fractions eluted with 10-20% ether-petroleum ether) and recrystallization from petroleum ether gave **3c**; m.p. 49-49.5°; ir (neat): 1725, 1720 cm⁻¹; vpc (10% SE-30, 213°, teflon-aluminum column) one peak 2.3 minutes; nmr (carbon tetrachloride): δ 1.05 (d, 3, C₈-CH₃), 1.0-2.0 (m, 10, ring H), 2.1, 2.2 (2d, 3, C₁₁-CH₃), 2.3 (m, 5, C₂-6,8-H), 5.1 (m, 1, O-CH).

Anal. Calcd. for C₁₃H₂₂O₃: C, 68.99; H, 9.80. Found: C, 69.18; H, 9.59.

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