## TERPENOIDS—CXXXVII:

# FRAGMENTATION OF COSTUNOLIDE AND ITS DERIVATIVES UNDER ELECTRON-IMPACT\*

## (MISS.) R. N. SATHE, G. H. KULKARNI, G. R. KELKAR and K. G. DAS National Chemical Laboratory, Poona-8, India

(Received 22 May 1969; accepted 12 June 1969)

Abstract—An attempt has been made to correlate the fragmentation modes and structure of costunolide and some lactones derived from it, containing a ten-membered carbocyclic system. The possible origins for the major fragments have been determined, using high resolution mass spectrometry and deuterium labelling.

Mass spectra of aliphatic lactones,<sup>1.2</sup> (—)santonin and its derivatives<sup>3.4</sup> have been recently investigated. However, the behaviour under electron-impact of sesquiterpenic  $\gamma$ -lactones, with a ten-membered carbocyclic system, does not seem to have received much attention. Costunolide is the parent lactone of such a group and the present communication deals with the fragmentation of some of its derivatives. From costunolide (I), the lactones (II),<sup>5</sup> (III),<sup>†</sup> (IV),<sup>†</sup> (V)<sup>5</sup> and (VI)<sup>6</sup> were prepared by known procedures.

A comparative study of the mass spectra of lactones I to IV, has revealed some common fragmentation modes and a few significant differences of diagnostic value in structure elucidation. The thermal rearrangement<sup>7</sup> of II and the transannular acid catalysed cyclization<sup>8,9</sup> of I and II are known. In order to explain satisfactorily some electron-impact induced fragmentation modes, observed in I, II and IV, it is necessary to assume that similar processes are operating in the vapour state. Table 1 gives the relative intensities of some significant ions observed in the spectra of these lactones.

In unsaturated lactones I to IV, the double bond appears to trigger the primary fragmentation processes. Depending on its location, differences are observed in the fragmentation patterns or in the relative intensities of some fragments. Sometimes, the migration of double bonds induced by electron-impact, alters the expected fragmentation reactions leading to unexpected cleavages.<sup>10</sup>

The insignificant value of the  $[M - CH_3]$  ion in V, suggests that the contribution from the methyl groups at  $C_4$ ,  $C_{10}$  and  $C_{11}$ , to the formation of this ion is negligible. This ion is, however, significant in the lactones I to IV, which is difficult to rationalise. The intensities of these ions in II and IV are comparable with that observed in (-)santonin (33%), where the major contribution has been proposed to come from the angular methyl group. A concerted cyclization mechanism leading to the elimination of a methyl radical, appears to contribute considerably to the formation of this ion in II and IV (Scheme 1).

\* Communication No. 1356.

<sup>†</sup> R. N. Sathe, G. H. Kulkarni and G. R. Kelkar, unpublished data.

<sup>1</sup> 

	(I)	(II)	(III)	(IV)	(V)
[M] <sup>+</sup>	27.6	100.0	90.8	97.8	4.8
[M - 15]+	8.7	32.0	<b>9</b> ·7	27.1	<1
[M - 28]+	<b>4</b> ∙0	2.3	1.0	27.1	17.7
[M - 43] <sup>+</sup>	7.8	11.3	<b>5</b> ·5	100.0	3.8
[M - 57] <sup>+</sup>	11.9	4.3	5.9	73·0	1.4
[M - 71] <sup>+</sup>	12.5	5.3	10 <b>0</b> ·0	75.0	2.8
[M - 73] <sup>+</sup>	7.6	38.0	33.5	64.6	21.2
[M - 85] <sup>+</sup>	15.1	5.0	33.0	63·0	1.9

TABLE 1. PERCENTAGE RELATIVE INTENSITIES



) Million

(IV)

mm

Ò







D

0





0

c⊳₀



ō

0 II

D D-





SCHEME 1

In lactone III, such a concerted mechanism cannot lead to the elimination of a methyl radical. The known tendency of lactone I to polymerize even at room temperature makes it difficult for an absolute comparison.

The loss of carbon monoxide from the lactone moiety has been shown to be a minor fragmentation mode.<sup>1</sup> The lower intensities of [M - 28] ions in the spectra of II and III corroborate this fact. The slightly higher intensity of this ion in I, however, is probably due to the presence of the conjugated *exo*-cyclic double bond. Similar observations were made in the spectra of some conjugated pseudo-guaiano-lides. In lactone IV, the major contribution to this ion is likely to come from the loss of  $C_2H_4$ , which is supported by high resolution data.

The [M - 43] ion seems to result from the successive loss of 15 and 28 mass units. The relative intensities of these fragments more or less follow a similar pattern as the [M - 15] and [M - 28] ions.

Another significant fragmentation mode observed in II, III and IV, is the loss of 56 and 57 mass units. In the spectrum of VI, this loss was found to be 86 and 87 mass units respectively. The genesis of these fragments can be rationalised by assuming the loss of  $C_3H_4O$  and  $C_3H_5O$  from the lactone moiety by  $\alpha$ -cleavage. A similar mechanism has been suggested to operate to some extent, in (-)santonin.

The origin of [M - 71] and [M - 73] ions which are also observed in the spectra of unsaturated and saturated keto lactones (VII) and (VIII) is discussed later. Deuteration and high-resolution data have been obtained to support the mechanisms suggested for the formation of these ions in (VII) and (VIII). Similar mechanisms can operate in lactones I to IV. Figures 1 to 6 show the mass spectra of these lactones.

#### Unsaturated keto lactone (VII)

The presence of a carbonyl group in a molecule has a great influence in initiating the primary fragmentation modes. As expected, the stability of the molecular ion is considerably reduced (II, 100%; III, 90.8% and VII, 19%).









The loss of a  $CH_3$  radical is not significant (1.5%), suggesting that a cyclization mechanism is not a favoured process.

The loss of  $H_2O$  (4.16%) can arise from (a) carbonyl group at  $C_1$  and (b) the lactone ethereal oxygen as suggested by McFadden *et al.*,<sup>1</sup> due to the availability of a hydrogen atom for a favourable transfer. Since, in lactones I to IV, this loss is negligible (<1%), it appears that the major contribution to this ion in VII is from the carbonyl group.

The loss of 28 mass units appears to be mostly due to carbon monoxide, since the same loss is observed in the deuterated compound IX. This is further confirmed by high resolution data.

One of the characteristic fragmentation modes of cyclic  $\alpha,\beta$ -unsaturated ketones<sup>11</sup> is the intense [M - 42] (C<sub>2</sub>H<sub>2</sub>O) peak. This process is relatively insignificant (1.8%) in the fragmentation of VII. Since this fragment is shifted by only one mass unit in the tri-deuterated analogue, the carbon atoms C<sub>1</sub> and C<sub>2</sub> are involved in the process.



A rearrangement process leading to the expulsion of carbon dioxide operates n VII to a small extent. The spectrum of the deuterated analogue shows the same loss. In this respect, it resembles (—)santonin.



#### SCHEME 3

The fragmentation reactions leading to the loss of 56 and 57 mass units appear to be very complex processes. Attempts were made to analyse these fragments to find out the contribution from various competing processes. Deuteration and high resolution studies indicated that this fragmentation mode is due to the loss of both  $C_3H_4O$  and  $C_4H_8$ . This is followed by the loss of one hydrogen atom to give the [M - 57] ion. The elimination of  $C_3H_4O$  can take place either from the lactone moiety as mentioned earlier in lactones II to IV or from the ten-membered ring involving carbon atoms  $C_1$ ,  $C_2$  and  $C_3$ . Similarly, the  $C_4H_8$  fragment can be lost in two different ways as indicated over. The loss of 56 mass units due to 2CO is of minor significance.



#### **SCHEME 4**

It is not possible to assume the formation of m/e 179 [M – 71] fragment by a successive loss of 56 and 15 mass units as in santonin. Since, the same loss is observed in the deuterated analogue, one of the possible mechanisms seems to be the elimination of a  $C_3H_3O_2$  fragment from the lactone moiety. Such a mechanism involves migration of the  $C_{11}$ -hydrogen atom to the remaining part of the molecule. The contribution from  $C_4H_7O$  and  $C_5H_{11}$  losses are of minor significance.



The loss of  $C_3H_5O_2$  (73 mass units) in (-)santonin has been confirmed by high resolution data.<sup>4</sup> Boocock *et al.*<sup>3</sup> invoked a methyl migration to explain this fragmentation process, which later appeared unnecessary.<sup>12</sup> It was suggested, however, that the process is triggered by removal of one of the  $\pi$ -electrons from the  $C_4$ -- $C_5$ double bond. We have now observed that this process is a characteristic fragmentation mode of many sesquiterpenic lactones,\* in which a hydrogen atom (from either  $C_4$ -methyl or  $C_8$ -methylene) is available for transfer to the ethereal lactone oxygen through a six-membered transition state. Table 2 shows the relative intensities of the [M - 73] ion in lactones II to VIII.

TABLE 2							
	(II)	(III)	(IV)	(V)	(VII)	(VIII)	(-)Santonin
[M - 73] <sup>+</sup>	38%	33.5%	64·6%	21.2%	17.2%	10.7%	90·6 <i>%</i>

\* K. G. Das and M. S. B. Nair, unpublished data on furanogermacranolides.

It is obvious from the table that the presence of double bond in the  $C_4$ — $C_5$  position is not a rigid structural requirement for this process, though it does facilitate such a reaction. Although both lactones II and IV fulfil these structural requirements, the intensity of this ion is lower in II than in IV. This can only be rationalised by assuming that a competing cyclization mechanism, involving this double bond, is operating in II to a greater extent, as suggested earlier for the loss of methyl.

In compound VI, which contains a  $-CH_2OCH_3$  group at  $C_{11}$ , instead of a loss of 73, a loss of 103 ( $C_4H_7O_3$ ) mass units is observed, while in the deuterated analogue the loss was shifted to 74 mass units. Hence, both  $C_{11}$  and  $C_{13}$  carbon atoms are involved in the loss.

The m/e 168 ion [M - 82] can arise by cleavage  $\alpha$ - to the carbonyl and  $\beta$ - to the double bond as indicated. Since the fragment with mass 82 (79%) is prominent, it is probable that the charge is carried by both the fragments. The m/e 167 ion may be considered to be formed by a rearrangement process, involving the transfer of a hydrogen atom to the C<sub>1</sub>-carbonyl, resulting in the rupture of the C<sub>1</sub>-C<sub>2</sub> bond, followed by cleavage of the C<sub>7</sub>-C<sub>8</sub> bond. Deuteration studies indicate that these peaks are shifted by 3 mass units, indicating that the hydrogen atoms at C<sub>2</sub> and C<sub>11</sub> are not participating in the process.





The successive loss of 73 ( $C_3H_5O_2$ ) and 28 (CO) mass units, satisfactorily explains the genesis of the m/e 149 ion, which was shifted to m/e 151 in the spectrum of the deuterated analogue.

$$[M]^+ \xrightarrow{-C_3H_5O_2} m/e \ 177 \xrightarrow{-CO} m/e \ 149$$

High resolution data indicated that the peak at m/e 122 is a doublet comprising  $C_8H_{10}O$  and  $C_9H_{14}$  ions in the ratio 10:1. On deuteration this peak is partly shifted to m/e 123, while a considerable portion remains unaffected. The ion  $C_9H_{14}$  can arise by the successive loss of 71 ( $C_3H_3O_2$ ) and 57 ( $C_3H_5O$ ) mass units.

The ion  $C_8H_{10}O$  can result by two different mechanisms involving hydrogen transfer, which corroborate the data obtained by deuteration studies.



SCHEME 7

The peak at m/e 95 (base peak) is also a doublet, comprising of C<sub>7</sub>H<sub>11</sub> and C<sub>6</sub>H<sub>7</sub>O in the ratio 3:1. In the spectrum of the deuterated compound it is partly shifted to m/e 96. One of the possible mechanisms for the formation of a C<sub>7</sub>H<sub>11</sub> ion which can shift by one mass unit on deuteration is shown below.



A loss of 73 ( $C_3H_5O_2$ ) followed by 82 ( $C_5H_6O$ ) mass units explains the formation of this ion (m/e 95) to some extent, which is supported by the spectrum of the deuterated version of VII.

### Ketolactone (VIII)

The spectrum of the saturated ketolactone (VIII) shows more or less similar fragmentation modes as in VII as regards the loss of 15, 18, 28, 43, 44, 56, 57, 71, 73 mass units. Differences are observed in the relative intensities of these fragments, however, (Table 3).

	(VII)	(VIII)
[M]+	19%	20%
[M – 15]+	1.5%	1%
$[M - 28]^+$	4.16%	2.1%
[M - 43]+	3.12%	1.3%
[M - 44]+	1.25%	2.9%
[M - 56]+	4.58%	2.0%
[M - 57]+	5.0%	8.3%
[M - 71] <sup>+</sup>	4.37%	8.0%
[M - 73]+	17.29%	10.58%

TABLE 3. RELATIVE INTENSITIES

The [M - 42] ion (characteristic of  $\alpha,\beta$ -unsaturated ketones) is absent. The loss of 83 mass units observed in VII has now become 85 mass units as anticipated.

The base peak is at m/e 125. The spectrum of the tetradeuterated analogue indicates, that it is partly shifted by one and two mass units respectively while a considerable portion remains unaffected. A possible mechanism which explains the shifting of this ion by two mass units in the deuterated compound is given below.



SCHEME 9

#### **EXPERIMENTAL**

Lactones II<sup>5</sup>, VII<sup>13</sup>, VIII<sup>13</sup> were prepared from costunolide (I)<sup>5</sup>, isolated from Saussurea lappa, Clarke.

The tetrahydrocostunolides, (III)\* and (IV)\* were obtained by partial hydrogenation of II, and separated by extensive chromatography over alumina and  $AgNO_3$ -impregnated silica gel. The structures of these compounds have been established from spectral data and chemical reactions.

Complete hydrogenation of III gave V.

\* R. N. Sathe, G. H. Kulkarni and G. R. Kelkar, unpublished data.

#### Deuteration of VII and VIII

It was carried out by repeatedly equilibrating VII with  $CH_3OD$  and Na to yield a mixture IX consisting of 60% trideuterated, 34% di-deuterated and 6% monodeuterated analogues (mass spectral analytical data). The deuterated analogue from VIII was similarly obtained and consists of 27% tetradeuterated, 37% trideuterated, 23% dideuterated, 11% monodeuterated and 2% unchanged VIII.

All mass spectra were run at a resolution of approximately 1000, on a CEC 21-110B mass spectrometer, at a source temperature of less than 150° using a direct inlet system. Precise mass measurements were performed by the peak matching technique at a resolution of 8000.

#### REFERENCES

- 1. W. H. McFadden, E. A. Day and M. J. Diamond, Anal. Chem. 37, 89 (1965).
- 2. L. Friedman and F. A. Long, J. Am. Chem. Soc. 75, 2832 (1953).
- 3. D. G. Boocock and E. S. Waight, Chem. Commun. 90 (1966).
- 4. N. Wasada, T. Tsuchiya, E. Joshii and E. Watanabe, Tetrahedron 23, 4623 (1967).
- 5. A. S. Rao, G. R. Kelkar and S. C. Bhattacharyya, Tetrahedron 9, 275 (1960).
- 6. G. H. Kulkarni, A. Paul, A. S. Rao, G. R. Kelkar and S. C. Bhattacharyya, Tetrahedron 12, 178 (1961).
- 7. A. S. Rao, A. Paul, Sadgopal and S. C. Bhattacharyya, Tetrahedron 13, 319 (1961).
- 8. G. H. Kulkarni, G. R. Kelkar and S. C. Bhattacharyya, Tetrahedron 20, 2639 (1964).
- 9. A. M. Shaligram, A. S. Rao and S. C. Bhattacharyya, Tetrahedron 18, 969 (1962).
- 10. D. S. Weinberg and C. Djerassi, J. Org. Chem. 31, 115 (1966).
- 11. H. Budzikiewicz, C. Djerassi and D. H. Williams, Interpretation of Mass Spectrometry of Organic Compounds, Holden-Day, San Francisco, 1967, p. 151.
- 12. H. Budzikiewicz, C. Djerassi and D. H. Williams, Interpretation of Mass Spectrometry of Organic Compounds, Holden-Day, San Francisco, 1967, p. 206.
- 13. Miss R. N. Sathe, G. H. Kulkarni and G. R. Kelkar, Indian J. Chem. 6, 122 (1968).