

THE STRUCTURE OF MELLITOXIN

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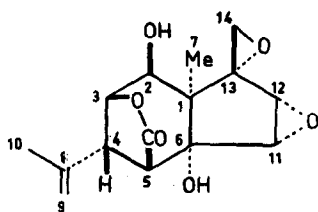
and

J.S. Shannon

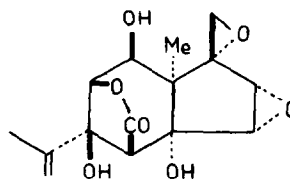
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MELLITOXIN, a metabolite produced by the insect Scolypops australis feeding on the leaves and stems of Coriaria arborea, was first isolated¹ from honey and given the formula $C_{15}H_{18}O_7$. Because of its mode of formation and biological activity² it seemed likely that it was an oxygenated derivative^{3,4} of tutin (I). The presence of three hydroxyl groups in mellitoxin was demonstrated by an infrared absorption band at 3600 cm^{-1} in its diacetate. Mellitoxin had absorption at 1645 cm^{-1} , which was not shown by dihydromellitoxin (m.p. $265-268^\circ$); and the formation of bromomellitoxin ($C_{15}H_{17}BrO_7$), analogous with bromotutin and bromopicrotoxinin, suggested a similar relation of a double bond to a hydroxyl group. Since bromomellitoxinone (m.p. $223-225^\circ$) had absorption in chloroform at 3600 and 1730 cm^{-1} it follows that two of the hydroxyl groups in mellitoxin are similar to those in tutin, while the third is probably tertiary.

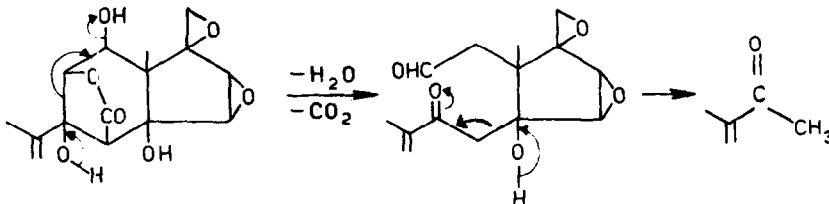


I



II

These observations suggest that mellitoxin is a hydroxytutin and, since it does not react with sodium periodate, it must possess the structure II. This assumption has been supported by mass-spectral evidence (see below) and by the reactions of mellitoxin and dihydromellitoxin with alkali, which gave methyl isopropenyl ketone and methyl isopropyl ketone, isolated in yields of 14% and 7% respectively. These could have been formed as below. Tutin gave no volatile products under these conditions.



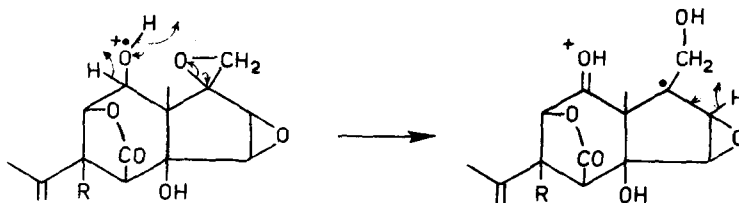
MASS SPECTRA

(i) Tutin (I) and Mellitoxin (II)

Evidence for structure II was obtained by comparison of the mass spectrum of tutin (I) with that of mellitoxin (II). The molecular weight of I was thus confirmed as 294; further, when I was exchanged with deuterium oxide within the ion source of the mass spectrometer⁵ the parent peak due to the molecular ion was shifted to m/e 296, thus indicating the presence in I of two hydroxyl groups. The spectrum of II did not show a parent peak; however, the

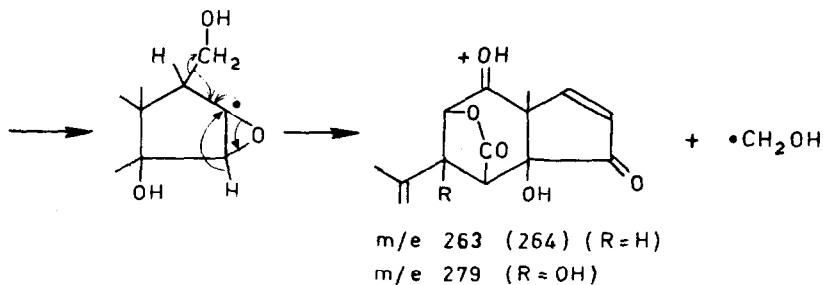
molecular weight of II was calculated as 310 since there was a peak at m/e 279 and a meta-stable peak at m/e 251.1 due to the transition $310^{\oplus} \rightarrow 279^{\oplus} + 31$. The peaks in the mass spectrum of II could be divided into two groups (Table 1): first, Group A, which was due to ions formed by corresponding reactions to those undergone by I; and, secondly, Group B, which was due to ion reactions involving those parts of the structure of I and II associated with the extra tertiary hydroxyl group in II at C-4. In the formulation of the proposed ion reactions below, the m/e values in brackets refer to corresponding peaks in the spectrum of I-O-d₂.

Group A peaks. - Both spectra had the expected M-15 and M-18 peaks due to the presence of an angular methyl group and hydroxyl groups respectively. The M-31 peaks at m/e 263 and at m/e 279 in the spectra of I and II were unusual since such peaks are normally associated with the loss as radicals of hydroxy methylene groups^{6,7}. However, Dreiding models showed that these latter groups could be formed by rearrangement of the molecular ions involving hydrogen transfer from the hydroxyl group at C-2 to the oxygen atom of the spiro ethylene oxide ring, especially if the latter ring was at first cleaved.



I m/e 294 (296) (R=H)

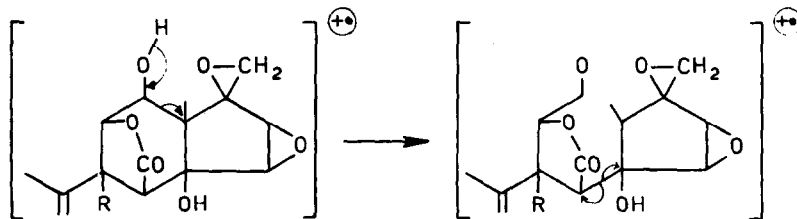
II m/e 310 (R=OH)



m/e 263 (264) (R=H)

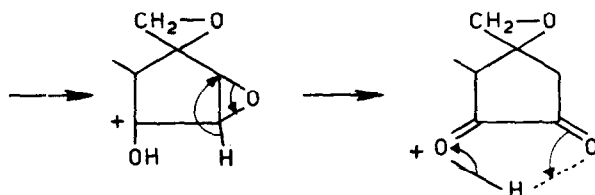
m/e 279 (R=OH)

The most intense (base) peaks in both spectra were at m/e 141; these peaks may be due to fission accompanied by hydrogen transfer^{7,8} of the six-membered ring.



I m/e 294 (296) (R = H)

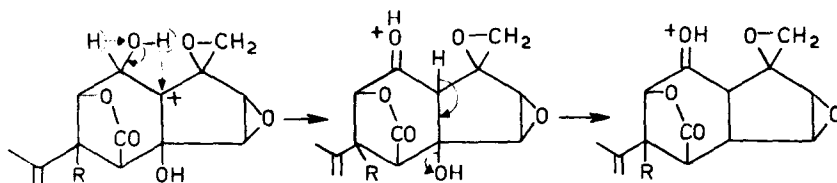
II m/e 310 (R = OH)



m/e 141 (142) (R = H)

m/e 141 (R = OH)

In both spectra the peaks at m/e 261 and at m/e 277 are of interest, since the former was not shifted in the spectrum of I- $O-d_2$, and a meta-stable peak at m/e 244.2 in the spectrum of I indicated the transition $279^{\oplus} \rightarrow 261^{\oplus} + 18-$ that is, both hydroxyl hydrogen atoms were eliminated as H_2O despite the relative trans configuration of the hydroxyl groups in the molecular ion. The proposed ion reactions are as follows (a driving force may be the formation of the resonance-stabilized ion products):



m/e 279 (281) ($R = H$)

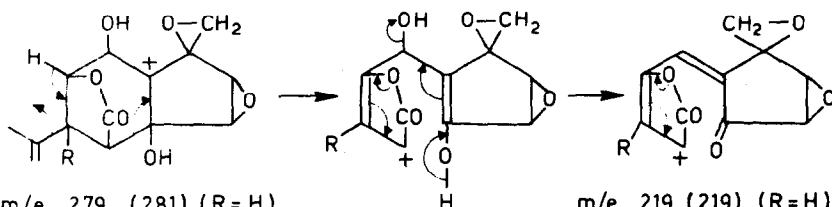
m/e 293 ($R = OH$)

m/e 261 (261) ($R = H$)

m/e 277 ($R = OH$)

For the loss of both hydroxyl hydrogen atoms it is necessary that one atom from the hydroxyl group at C-2, and not the C-2 hydrogen atom, be initially transferred to C-1. This proposal is consistent with 1,3-transfer processes being more favoured than the 1,2-type⁹.

The formation of the ion of mass 219 from I (and of mass 235 from II) also involved the loss of both hydroxyl hydrogen atoms. This may be due to a 1,4-elimination process, preceded by reactions leading to the formation of ions of mass 237 and 253 from I and II respectively. In these latter ions there had already been a departure from the rigid relation between the two hydroxyl groups.



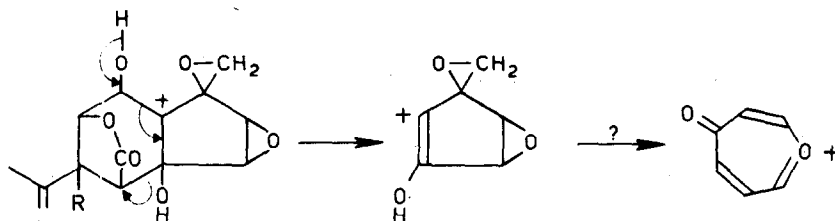
m/e 279 (281) ($R = H$)

m/e 295 ($R = OH$)

m/e 219 (219) ($R = H$)

m/e 235 ($R = OH$)

In the spectra of I and II the peaks at m/e 125, which were second in order of intensity to those at m/e 141, may have been due to the following reactions involving hydrogen shifts in the $M-15$ ions:



m/e 279 (281) (R=H)

m/e 125 (126) (R=H)

m/e 293 (R=OH)

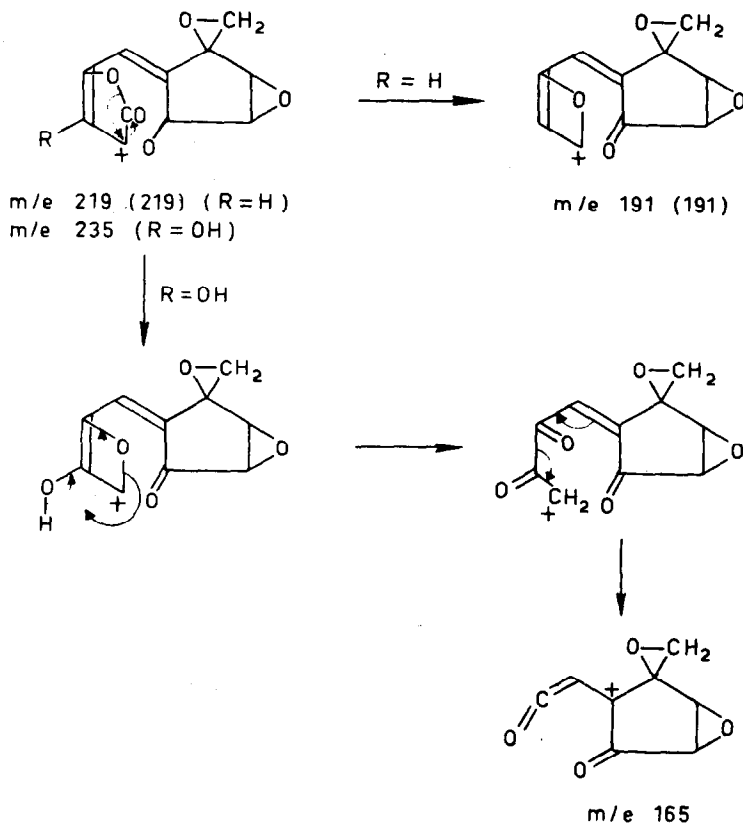
m/e 125 (R=OH)

It may be worthy of note that the structure of the ion of mass 125 is capable of rearrangement, to form either the ion shown or alternative stabilized ions.

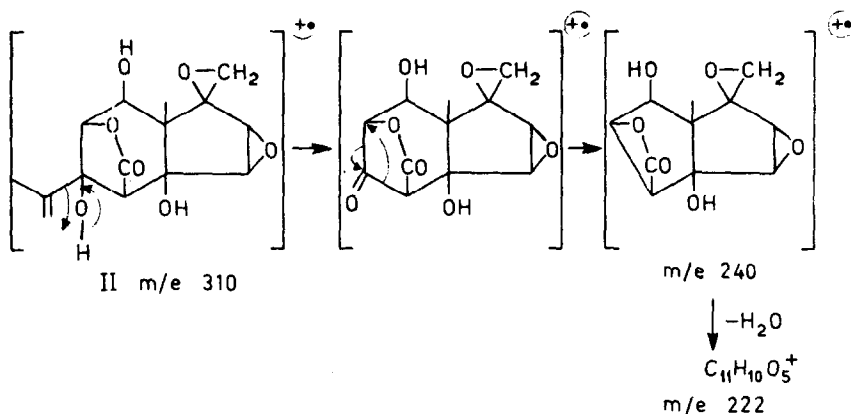
Similar extensive rearrangements of small-ring ions to form more stable larger-ring ions are known in ion reactions of hydrocarbons¹⁰.

The authors have thus correlated most of the important peaks (Group A) in the spectrum of I with its known structure. Further, for each of the peaks there is a corresponding peak in the spectrum of II if the presence is assumed in II at C-4 of an extra hydroxyl group.

Group B peaks. - These peaks, which are associated with the parts of the molecules containing the extra hydroxyl group in II, may be assigned ion structures if the latter group is attached at C-4. First, for example, the peak at m/e 191 in the spectrum of I and the peak at m/e 165 in the spectrum of II may be due to the following ion reactions:

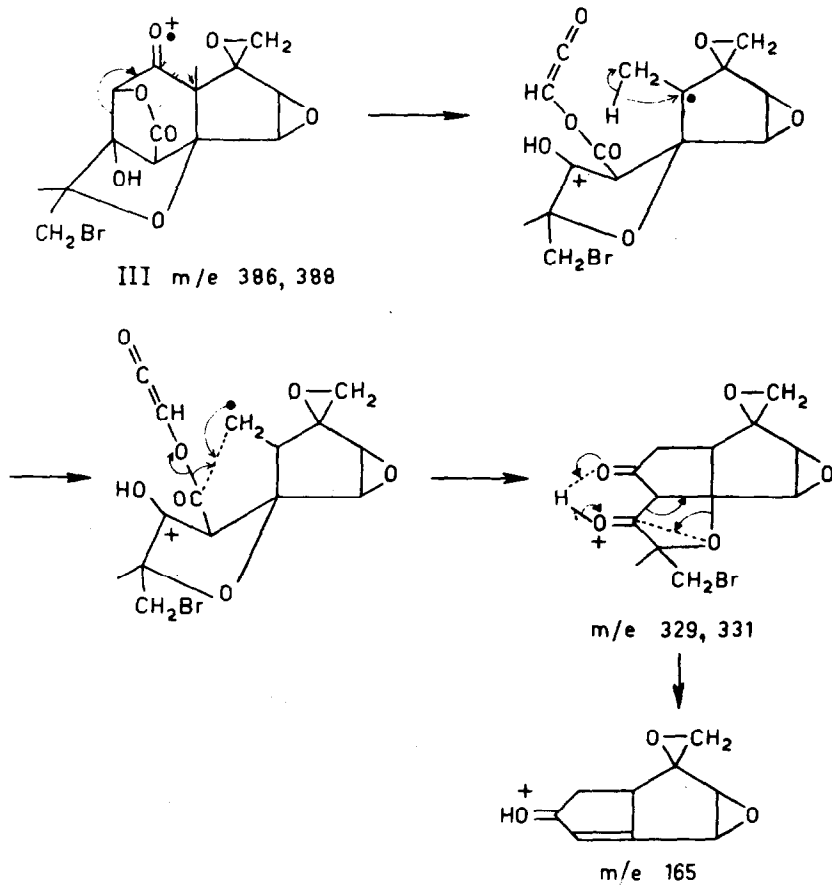


Secondly, the peaks at m/e 240 and m/e 222, which are associated only with the spectrum of II, may be due to the following reactions (a meta-stable peak at m/e 205.3 confirmed the occurrence of the transitions $240^{\oplus} \rightarrow 222^{\oplus} + 18$):



(ii) Bromomellitoxinone (III)

The mass spectrum of III confirmed its molecular weight as 386 (Br = 79). Further, the presence of one bromine atom was confirmed by the fact that the two isotopic peaks at m/e 386 and m/e 388 were of equal height¹¹. The spectrum of III-O-d (the latter was prepared in the usual way by exchange with deuterium oxide within the ion source) showed a shift of one mass unit in the parent peaks, thus confirming the presence of one hydroxyl group. All the peaks due to ion fragments, except those at m/e 329 and m/e 331, were due to bromine-free ions and possibly arose from initial homolytic fission of the bond adjacent to the C-2 keto group. A meta-stable peak at m/e 281.4 corresponded to the transitions $386^{\oplus}, 388^{\oplus} \rightarrow 329^{\oplus}, 331^{\oplus} + 57$. This reaction may be formulated as depicted below; the ion product may further dissociate into an ion of mass 165 (corresponding to the base peak of the spectrum).



Peaks at m/e 307 (M-Br) and m/e 293 (M-CH₂Br) indicated the presence of a -CH₂Br group.

Table 1

	I	I-O-d ₂	II
m/e values	294(0.3)*	296	
	279(1.2)	281	295(0.2)*
	276(1.5)	277	292(3.1)
	263(2.8)	264	279(0.9)
Group A	261(1.8)	261	277(3.1)
	237(0.9)	239	253(1.9)
	219(7.0)	219	235(4.5)
	141(100.0)	142	141(100.0)
	125(73.5)	126	125(91.5)
Group B	191(13.6)	191	240(3.5)
			218(1.2)
			165(30.0)

* Percentage proportion of base peak at m/e 141.

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