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MASS SPECTROMETRY OF STEROID SYSTEMS—IV*

CIS-TRANS ISOMERISM OF DI- AND TRICYCLIC MODEL COMPOUNDS

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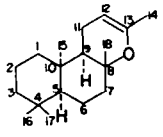
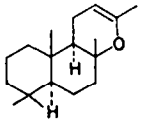
Abstract—The fragmentation behaviour of *cis*(I)- and *trans*-A/B-sclareoloxide (II) and of *cis*(III)- and *trans*-2,5,5,1a-tetramethyl-1a,4a,5,6,7,8-hexahydro-γ-chromene (IV) upon electron bombardment has been investigated. It has been found that the intensity differences between the molecular ion and characteristic fragment peaks in the mass spectra of the isomeric sclareoloxides and the corresponding chromenes provides a basis for *cis*- or *trans*-configurational assignments to these compounds.

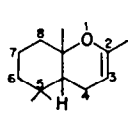
In continuation of the mass spectrometric investigation of the *cis-trans*-isomerism of polycyclic systems,[1] a study of the mass spectra of *cis*(I)- and *trans*-A/B-sclareoloxide (II) and their bicyclic analogs, namely, *cis*(III)- and *trans*-2,5,5,1a-tetramethyl-1a,4a,5,6,7,8-hexahydro-γ-chromene (IV) is reported. In order to interpret the fragmentation mechanism of sclareoloxides (I and II), the fragmentation of α-monocyclofarnesylacetone (V) (the starting material in the synthesis of I) has been investigated.



I



II



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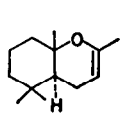
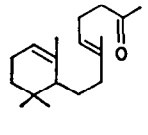


IV



V

I. *Sclareoloxides* (I *and* II)

The mass spectra of *trans*-sclareoloxide (II) and a number of related diterpenes have been described by English[2] and French[3] workers, but their conclusions regarding the fragmentation mechanism were derived only on general grounds. It was therefore

* Part III: V. I. Zaretskii, N. S. Wulfson, V. G. Zaikin, S. N. Ananchenko, V. N. Leonov and I. V. Torgov, *Tetrahedron* **21**, 2769 (1965).

† Laboratory of Mass Spectrometry.

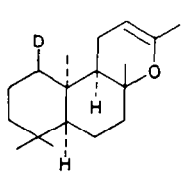
‡ Laboratory of Fine Organic Synthesis.

[1] V. I. Zaretskii, N. S. Wulfson, V. L. Sadovskaya, S. N. Ananchenko, I. V. Torgov, *Dokl. Akad. Nauk SSSR* **158**, 385 (1964).

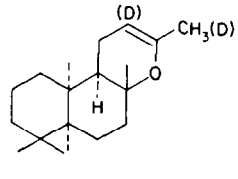
[2] R. Hodges and R. I. Reed, *Tetrahedron* **10**, 71 (1960).

[3] H. Audier, S. Bory, M. Fetison, *Bull. Soc. Chim. Fr.* 1381 (1964).

decided to obtain more convincing data on the course of the fragmentation of I and II by taking the mass spectra of their deuteroderivatives (VI and VII), with the label in different positions of rings A and C.



VI



VII

Molecular ion, M-15, *M*-15–18 *and M*-58 *peaks.* The spectra of sclareoloxides (I and II) display a prominent molecular ion peak (Figs. 1a, b). These compounds might have undergone a type of fragmentation similar to V, provided of course that their molecular ions could undergo a retro Diels-Alder reaction to yield the ion M_2^+. However, a comparison of the mass spectra of oxides I and II with that of V (Figs. 1a, b,

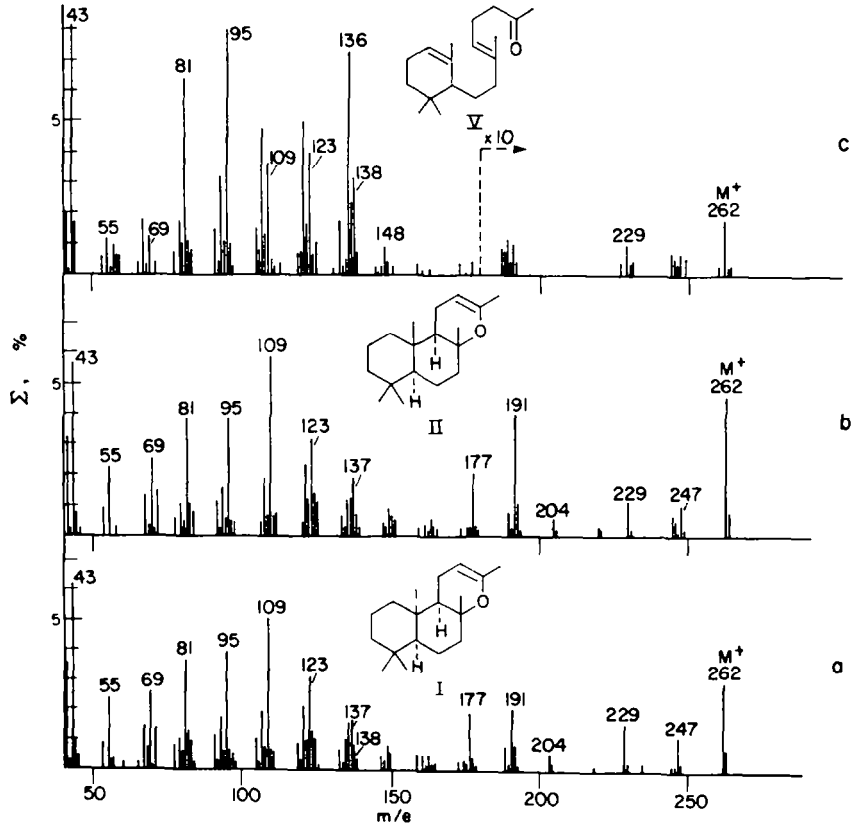
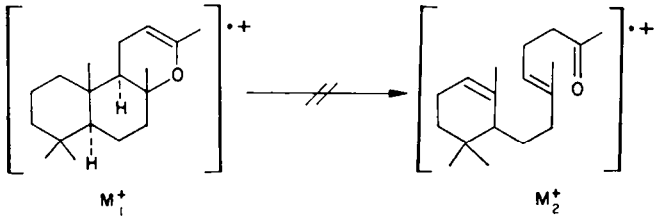


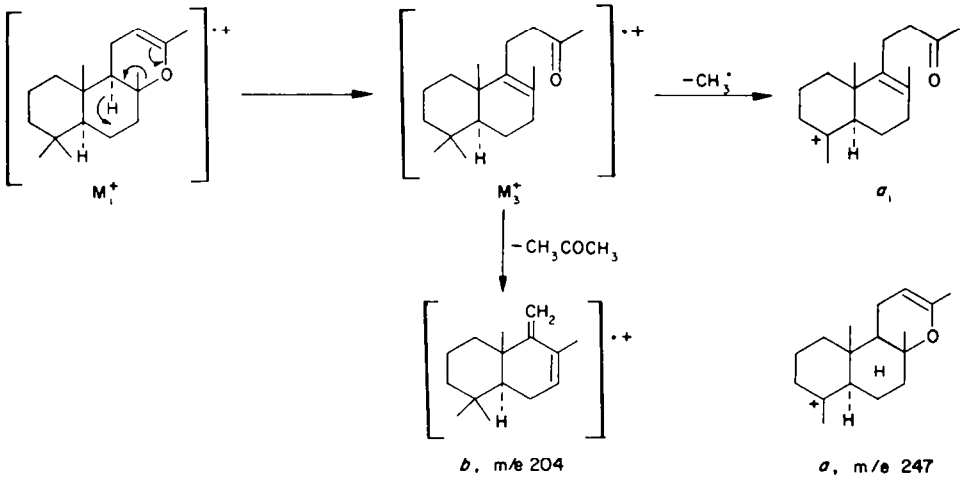
FIG. 1. Mass spectra of: (a) *cis*-A/B-Sclareoloxide (I) (b) *trans*-A/B-Sclareoloxide (II) (c) α-Monocyclofarnesylacetone (V)

c) has revealed essential differences despite a formal similarity, so that the aforementioned possibility of the simultaneous opening of rings B and C to yield the ion M_2^+ actually does not take place.



The molecular ions of oxides I and II lose water and a methyl radical giving the corresponding ion M-18 (m/e 244) and M-15 (fragment *a*, m/e 247). The fragment M-15 could result from elimination of methyl from positions 4, 8 or 10 but is due mainly to loss of methyl from position 4 as can be seen from the mass spectrum of *trans*-5-ethyl-2,5,1a-trimethyl-1a,4a,5,6,7,8-hexahydro-γ-chromene (IVa) which has a large M-29 but practically no M-15 peak. Elimination of water by the fragment *a* gives rise to the ion *a*-18 (m/e 229). The loss of water by ions M_1^+ and *a* is apparently accompanied by the opening of only ring C and the intermediate formation of the ketonic forms (M_3^+ and a_1, respectively) of the molecular ion and ion *a*. This is substantiated by the presence of M-18 and M-15–18 peaks in the spectrum of α-monocyclofarnesylacetone (Fig. 1c, cf.[4]). It also accounts for the formation of the ion M-58 (*b*, m/e 204) due to loss of acetone by the molecular ion M_3^+ (Scheme 1). The

Scheme 1

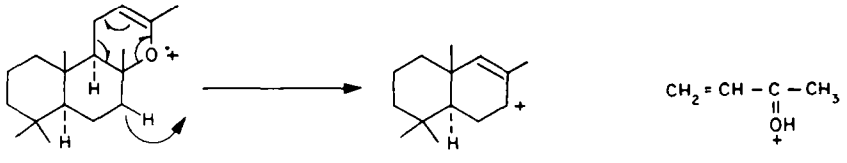


mechanism postulated for the formation of fragment *b* is confirmed by the mass spectra of the deuteroanalogs (VI and VII). In the latter the mass number of the ion *b* peak remains unchanged, whereas in the former the m/e value is shifted by a unit to m/e 205.

Peaks at m/e 191 *and* 177. Although most manoyloxide derivatives form a m/e 192

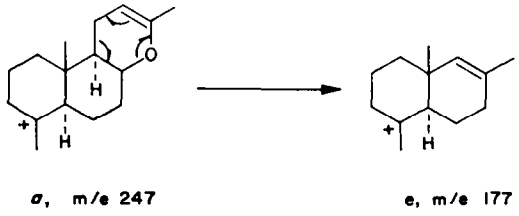
fragment upon electron bombardment[3] the spectra of I and II exhibit a strong peak at m/e 191 (fragment *c*), whereas that at m/e 192 is insignificant. Fragment *c* (Scheme 2) results from fracture of ring C by a retro Diels-Alder reaction and hydride ion migration to the neutral fragment. The same breakdown of ring C but with localization of the charge on the oxygen-containing fragment and migration to it of a hydrogen atom from the neutral fragment gives rise to ion *d* (m/e 71). The proof of the mechanism postulated for the formation of ions *c* and *d* is found in the mass spectra of the deuteroanalogs (VI and VII). The 50% shift of the *c* peak in VI (Table 1) shows that position 1 is a source of the migrating hydrogen. The *d* peak in the spectrum VI is shifted by a unit to m/e 72. However, this also occurs in VII, which is deuterated at positions 12 and 14, whereas there is no change in the mass number of the *c* peak in VII. Ion *e*

Scheme 2



(m/e 177) like fragment *c* results from the fragmentation of *a* by a retro Diels-Alder reaction (Scheme 3).

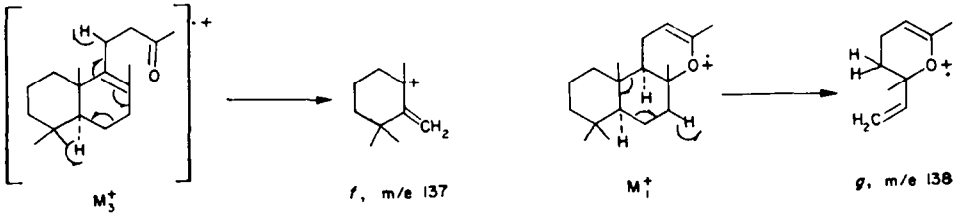
Scheme 3



Peaks at m/e 137 *and* 138. Fission of ring B in the molecular ion of I and II gives rise to fragments *f* (m/e 137) and *g* (m/e 138) retaining rings A and C, respectively (Schemes 4, 5). The structure of ions *f* and *g* is confirmed by the mass spectra of the deuteroanalogs (VI and VII). In the spectrum of VI the peak at m/e 137 is shifted by a unit to m/e 138 whereas the spectrum of VII exhibit equiintense peaks at m/e 138, 139 and 140.

Scheme 4

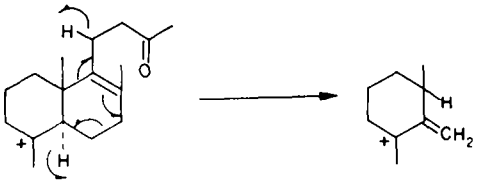
Scheme 5



[4] H. Budzikiewicz, C. Djerassi and D. Williams, *Structure Elucidation of Natural Products by Mass Spectrometry* Vol. 2, p. 160. San Francisco (1964).

Peak at m/e 123. Fragment *h* at m/e 123 contains ring A, as confirmed by the unit shift of the corresponding peak in the mass spectrum of VI to m/e 124. The fragmentation may be schematically represented as follows:

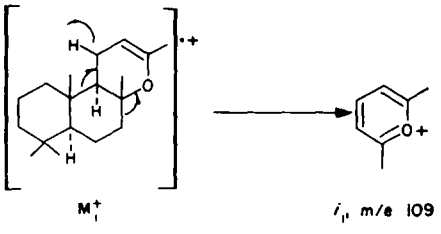
Scheme 6



a_1, m/e 247 *h*, m/e 123

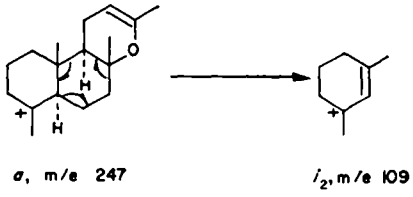
Peak at m/e 109. The presence of this peak in spectra of I and II is due to fragment i_1 and i_2 containing ring A and C, respectively (Schemes 7 and 8). Indeed the spectra of VI and VII show partial shift of this peak to m/e 110, that of VI being more pronounced.

Scheme 7



M_1^+ i_1, m/e 109

Scheme 8



a, m/e 247 i_2, m/e 109

Peak at m/e 95. The probable mechanism of formation of fragment *j* (m/e 95, Scheme 9) involves loss of an ethylene molecule from ion *h* due to a retro Diels-Alder reaction, since there is practically no shift of the m/e 95 peak in the spectra of VI and VII. Evidently ion *j* does not contain either ring C or atom C-1.

Scheme 9

h, m/e 123 *j*, m/e 95

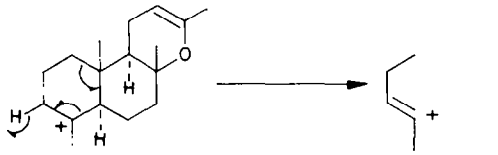
Peak at m/e 81. Contrary to fragment *j*, the m/e 81 peak (*k*) in the spectrum of VI undergoes unit shift to m/e 82 (Table 1) whereas no shift of *k* occurs in the spectrum of VII. This shows that fragment *k* contains the elements of ring A, including C-1. The mechanism of formation of fragment *k* (Scheme 10) could be similar to that described above for ion *j*.

Scheme 10

I_2, m/e 109 *k*, m/e 81

Peak at m/e 69. The m/e 69 fragment must contain atom C-1 since the mass number of the corresponding peak in the spectrum of VI is displaced by a unit to m/e 70 (Table 1) and is apparently due to rupture of ring A in ion *a*:

Scheme 11



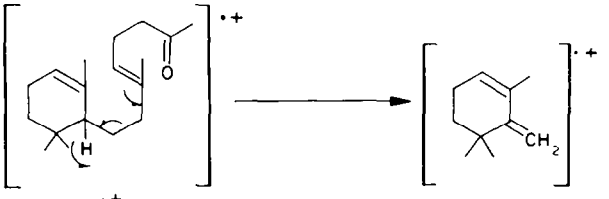
a, m/e 247 *l*, m/e 69

II. *α-Monocyclofarnesylacetone*

The mass spectrum of α-monocyclofarnesylacetone (V) (Fig. 1c), contrary to the cyclic analog I, shows very low intensities for peaks of the ions M_2^+, M-15 and M-15–18, the most prominent peaks being in the region of lower mass numbers.

Peaks at m/e 136 *and* 138. The structure of fragment *m* at m/e 136 (Scheme 12) is similar to that of ion *f* at m/e 137 (Scheme 4).

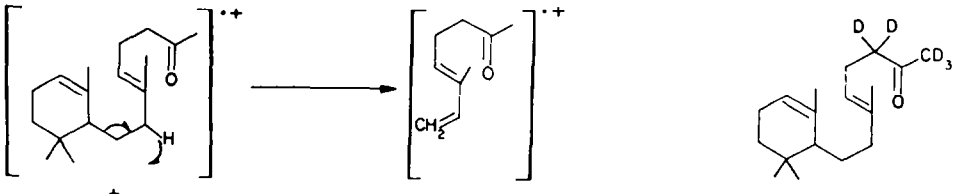
Scheme 12



M_2^+ *m*, m/e 136

Ion *n* at m/e 138 results from fission of the side chain α–C bond with the ring, accompanied by charge localization on the oxygen-containing fragment and loss by the latter of a hydrogen atom (Scheme 13). This is confirmed by the spectrum of the pentadeutero-anolog (VIII), wherein the m/e 138 peak is completely displaced by five mass units (to m/e 143).

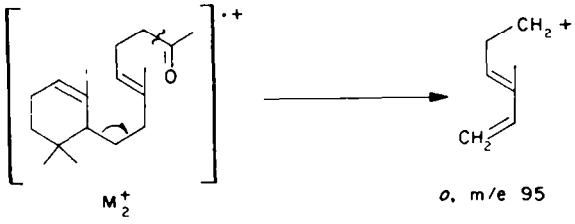
Scheme 13



M_2^+ *n*, m/e 138 VIII

Peak at m/e 95. The m/e 95 peak is apparently due to fragments resulting from two processes, one of which leads to the ion *o* (Scheme 14) with a methylene group adjacent to CO. This is substantiated by partial shift of the m/e 95 peak (ion *o*) in the spectrum of VIII, giving two equivalent peaks at m/e 95 and 97.

Scheme 14



Peak at m/e 43. This is due to an acetyl ion which contains the methyl group adjacent to the carbonyl function in α-monocyclofarnesylacetone, in good accord with displacement of the corresponding peak by three mass units (to m/e 46) in the spectrum of VIII.

III. 2,5,5,1a-*Tetramethyl*-1a,4a,5,6,7,8-*hexahydro-γ-chromenes* (III *and* IV)

The mass spectra of chromenes (III and IV) reveal many features in common with those of their tricyclic analogs, viz. oxides (I and II). This may be due to basic fragmentation processes of the molecular ions which proceed with the formation of fragments containing the atoms derived from rings A or C. The only exception is the degradation to ions *c* (m/e 191) and *e* (m/e 177) characteristic of tricyclic diterpenes.

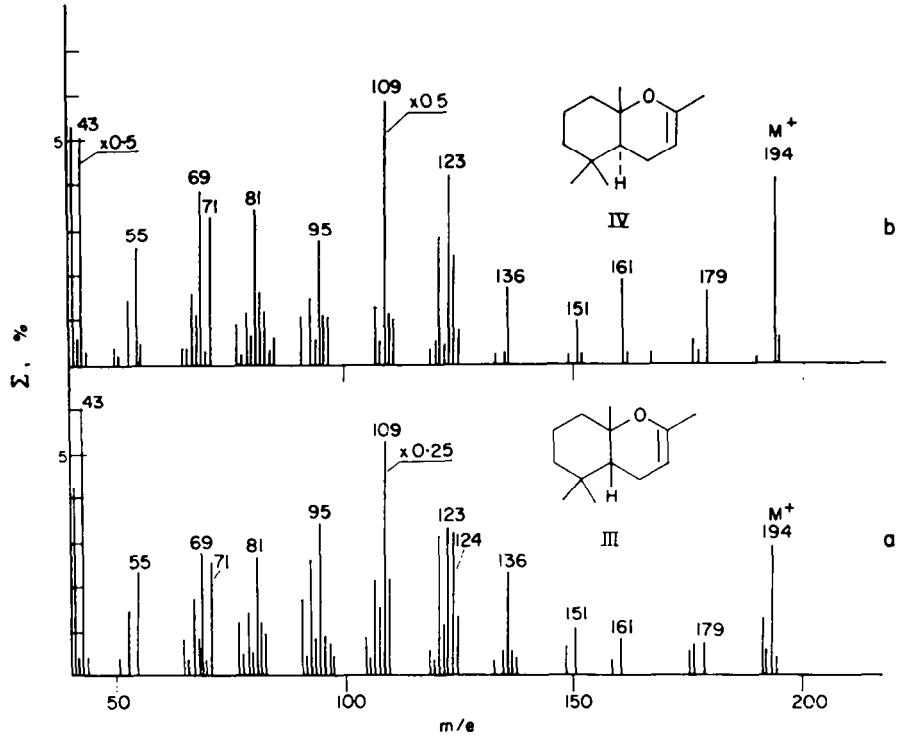
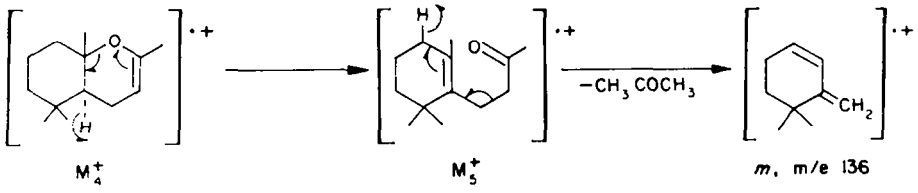
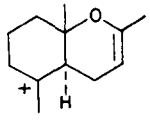


FIG. 2. Mass spectra of: (a) *cis*-2,5,5,1a-Tetramethyl-1a,4a,5,6,7,8-hexahydro-γ-chromene (III) (b) *trans*-2,3,5,1a-Tetramethyl-1a,4a,5,6,7,8-hexahydro-γ-chromene (IV)

The mass spectra of chromenes (III and IV) (Figs. 2a, b) just as those of sclareoloxides exhibit a prominent molecular ion (M_4^+) peak and peaks due to the ion *p* (M-15) and (M-15–18). The mechanism of formation of the latter as well as of (M-58) (*m*, m/e 136) is similar to that of corresponding ions in sclareoloxides I and II (Scheme 15).

Scheme 15

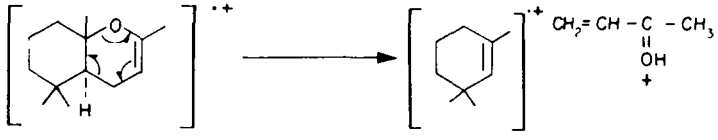




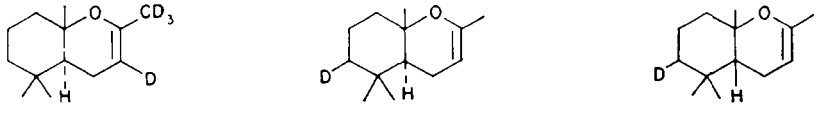
p, m/e 179

Peaks at m/e 124, 123 *and* 71. The m/e 124 and 123 fragments (*q* and *r*) apparently stem from the molecular ion by cleavage of bonds 1–1a and 4–4a, the formation of ion *r* proceeding with loss of a hydrogen atom from ring A (Scheme 16). The same molec-

Scheme 16



ular ion fragmentation accompanied by charge localization on the oxygen-containing fragment gives rise to ion *d* at m/e 71. The mechanism of formation of ions *q*, *r* and *d* is confirmed by mass spectra of chromene deuteroanalogs (IX, X and XI). In X and XI the peaks of ions *q* and *r* are displaced by a unit to m/e 125 and 124, respectively

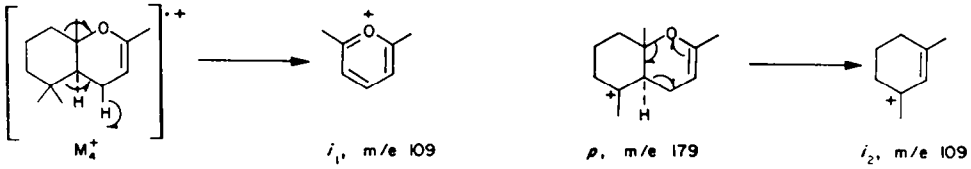


IX X XI

whereas in the IX the mass number of these peaks remains unchanged. In contrast to the m/e 124 and 123 peaks the m/e 71 peak (ion *d*) is displaced by three mass units (to m/e 74) in the spectrum of IX, and does not shift in the spectra of X and XI.

Peak at m/e 109. This is the base peak in the spectra of chromenes (III and IV). As with sclareoloxides the corresponding ion is formed by two routes leading either to the oxygen-containing fragment i_1 or to the hydrocarbon ion i_2 (Scheme 17). The

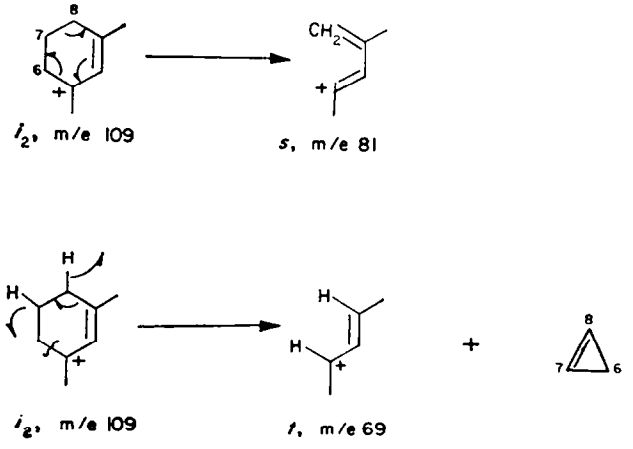
Scheme 17



second alternative (leading to ion i_2) predominates as confirmed by the spectra of IX and X (Table 2). The fact that the fragment i_2 results from ion *p* rather than from the molecular ion is in accord with the absence of shift of the m/e 109 peak in the spectra of IVa. It is to be noted, that ion i_2 may be formed not only on decomposition of ion *p* (M-15) but also from ion *q* on loss of a methyl radical. This is substantiated by the spectrum of the deutero-analog (XI) which reveals a metastable peak at m/e 97 (calc. 96·8) corresponding to the one step process m/e 125 → m/e 110 + 15.

The structure of the low mass number fragments (m/e 95, 81 and 69) containing like the sclareoloxides (I and II) the elements of ring A is somewhat different from that of the corresponding ions formed on fragmentation of I and II. Indeed, the spectrum of XI shows only a slight shift of the m/e 81 and 69 peaks to m/e 82 and 70. This indicates that the corresponding ions (*s* and *t*) do not contain the C-6 atom and their formation may proceed as follows (Scheme 18):

Scheme 18



The mass spectra of *cis*- and *trans*-2(3′-oxobutyl)-1,3,3-trimethylcyclohexanol semicarbazones show no molecular ion peak and proved to be identical with the spectra of the corresponding *cis*(III)- and *trans*-chromene (IV). This may be accounted for by cyclization of semicarbazones in the mass spectrometer inlet system (at 200°) to give III and IV.

TABLE 1

Compound	M^+	M-15	M^+-15–18	m/e_{204}	m/e_{191}	m/e_{177}	m/e_{109}	m/e_{95}	m/e_{81}	m/e_{69}	m/e_{71}
cis-Sclareol-oxide (I) Fig. 1a	262	247	229	204	191	177	109	95	81	69	71
trans-Sclareol-oxide (II) Fig. 1b	262	247	229	204	191	177	109	95	81	69	71
1-d_1-*cis*-Sclareol-oxide (VI)	262 26% 263 63% 264 11%	247 9% 248 62% 249 29%	229 32% 230 60% 231 8%	204 33% 205 60% 206 7%	191 39% 192 47% 193 14%	177 38% 178 50% 179 12%	109 58% 110 31% 111 11%	95 64% 96 23% 97 13%	81 12% 82 59% 83 29%	69 12% 70 88%	71 22% 72 68% 73 10%
d-*cis*-Sclareol-oxide (VII)	262 15% 263 32% 264 32% 265 21%	247 24% 248 62% 249 31% 250 11%	229 17% 230 36% 231 33% 232 14%	—	—	—	—	—	—	—	—

TABLE 2

Compound	M^+	M^+-15	M^+-15–18	m/e_{136}	m/e_{109}	m/e_{71}	m/e_{69}
trans-2,5,5,1a-Tetramethyl-1a,4a,5,6,7,8-hexahydro-γ-chromene (IV) Fig. 2b	194	179	161	136	109	71	69
trans-6-d_1-2,5,5,1a-Tetramethyl 1a,4a,5,6,7,8-hexahydro-γ-chromene (X)	194 36% 195 56% 196 8%	179 30% 180 70%	161 39% 162 61%	136 35% 137 65%	109 51 110 49%	—	69 70% 70 30%
trans-2(Trideutero-methyl)-3-d_1-2,5,5,1a-tetramethyl-1a,4a,5,6,7,8-hexahydro-γ-chromene (IX)	195 13% 196 39% 197 40% 198 8%	—	—	—	109 74% 110 6% 111 10% 112 10%	71 6% 72 13% 73 36% 74 39% 75 6%	

Stereochemistry

The structure of the *cis*-oxide (I) has not yet been fully established. Our results suggest that I has the same structure as II but differs from it as well as from naturally occurring sclareoloxide by the mode of fusion of rings A and B.

Stereochemical differences between *cis*(I)- and *trans*-sclareoloxide (II) are reflected mainly in a strong decrease in intensity of the molecular ion peak and increase of the peaks of ions (M-15) and (M-15–18) on passing from a *trans*- to a *cis*-isomer. This is apparently due to a small difference in energy in these isomers (cf. spectra of *cis*- and *trans*-decalin,[5] differing very little in the intensity of the molecular ion peaks and in those of the characteristic fragments). Now, the energy difference between *cis*- and *trans*-9-methyldecalin is much smaller than that of the isomeric decalins.[6] This accounts for the spectra of I and II in which the peaks of the fragments due to cleavage of the bonds at the junction of rings A and B, whose intensities were shown[1] to mirror the energy differences of the isomers, are practically of the same value. In contrast, in chromenes (III and IV) the *cis*(III)- and *trans*-isomer (IV) not only exhibit different intensities in the molecular ion peak [M^+ being more prominent in the spectrum of *trans*-chromene (IV)] but also in the m/e 109 peak due to fragments i_1 and i_2 (formed by cleavage of the bonds at the rings junction) which sharply gains in intensity on passing from *trans*-(IV) to *cis*-chromene (III). It is also known[7] that *trans*-chromene is much more stable than the *cis*-isomer, the equilibrium mixture at $-20°$ containing 80% of IV and 20% of III. It is possible that the energy difference between the *cis*- and *trans*-fused rings when one of the rings contains a hetero-atom is much larger than for the corresponding alicyclic compounds. This, however, requires further substantiation, which is now in progress.

EXPERIMENTAL

Mass spectra were taken on the commerical spectrometer MX-1303 provided with a glass inlet system heated to 120–175°, the electron energy being 70 eV.

Sclareoloxide (II) was prepared by a conventional procedure from natural sclareol[8] where the configuration has been strictly established. The *cis*-isomer (I) was prepared by stereo-specific cyclization from α-monocyclofarnesylacetone[9] and its *cis*-A/B-configuration was proved chemically and by the NMR spectrum. *cis*-1-d_1-Sclareoloxide (VI) was prepared by cyclization of V under usual conditions with D_2SO_4. The deutero-derivative (VII) was perpared by H_2SO_4 acid cyclization of the corresponding pentadeutero-α-monocyclofarnesylacetone (VIII), obtained from V by exchange with D_2O in dioxan in the presence of NaOH (100 hr, 80°). The individuality of the resultant oxides was established by GLC on polar and apolar phases. Similar procedures were used to prepare deutero-analogs of chromenes. Compound IX was obtained by H_2SO_4 induced cyclization of *trans*-pentadeutero-geranylacetone, X and XI were prepared from *trans*- and *cis*-geranylacetone, respectively, in the presence of D_2SO_4.

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