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# MASS SPECTROMETRIC STUDIES OF DITERPENES

## VIII—EPIMERS

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**Abstract**—Diterpene epimers differing with respect to orientation of a secondary hydroxyl group, ring fusion or configuration at an asymmetric centre carrying carbon–carbon linked substituents were studied, and certain stereostructural-spectral correlations were achieved for the first two groups. Each of the compounds examined was subjected to multiple scanning at both high and low electron voltage to allow computer assisted statistical calculation and comparison of intensity intervals at a predetermined confidence level for total ion currents and selected peaks.

## INTRODUCTION

A FAIR number of mass spectral studies of epimers have been published during the past decade, but relatively few have concerned terpenoids, despite the fact that terpene epimers are often encountered in nature and are frequently obtained during synthetic and degradative work.[1] Since most diterpenoids possess a rigid skeleton where even minor changes can alter steric interactions and intermolecular reactions, they provide an interesting test ground for mass spectrometric hypotheses derived from studies of simpler model compounds. Moreover, on account of their greater complexity they offer new combinations and competition between reactions not experienced in the simpler compounds.

Present knowledge about the utility of mass spectrometry for configurational assignments in the diterpene series is, however, limited to a few examples, i.e. to manoyloxide and some related compounds[2,3,4] and to $\alpha_1$- and $\alpha_2$- levantanolides.[5] In view of this and as an extension of our earlier studies[6] of the fragmentation reactions of certain groups of diterpenoids, we have examined some forty pairs of diterpene epimers to evaluate the importance of some commonly encountered steric factors. The results are discussed here as well as the applicability of the method to stereochemical problems in the diterpene series.

It is well known, notably from a critical review by Meyerson and Weitkamp,[1] that mass spectral differences between epimers may be associated with two types of processes; reactions depending on the attainment of a transition state of minimum energy content and reactions which are sterically controlled and directed by a functional group. The former reflect the differences in enthalpy or conformational energy between the epimers and the latter the different capability of the epimers to undergo certain fragmentation reactions involving stereospecific bond forming processes. In stereostructural-spectral correlation studies, the spectral differences are usually measured as intensity differences expressed as a percentage of the total ion current for the molecular and selected fragment ions, since this represents a convenient and rapid method. Although this approach, as discussed elsewhere,[1] is based on a number of assumptions some of which are probably not valid in all instances, it has

proved satisfactory in most cases when carefully applied and is used here as a basis for the correlation.

In contrast to earlier studies of epimers, where single intensity values have been used almost exclusively, several spectra of each compound—on the average ten—were recorded at both high and low electron voltage to allow calculation and comparison of intensity intervals at a predetermined confidence level. The obvious reason for using multiple scanning and statistical evaluation was to estimate and minimise the effects of commonly encountered variations in total ion intensity, $\sum_{40} I$,* and relative peak intensity, $I/\sum_{40} I$, between spectra of the same compound recorded on different occasions. This was of particular importance when the intensity differences between spectra of a pair of epimers are small and accordingly of doubtful value unless the significance of the difference is known. Since the epimers studied, which differ with respect to orientation of a hydroxyl group (1 to 32), ring fusion (33 to 50) or configuration at an asymmetric centre carrying carbon–carbon linked substituents (33 to 40, 46, 51 to 81), can conveniently be divided into three groups both on a chemical basis and according to the mass spectrometric results obtained, they are discussed below under three separate headings.

## RESULTS AND DISCUSSION

### *Alcohols*

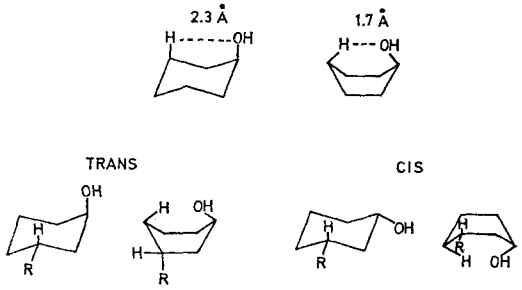
Previous detailed studies of electron-impact-induced water elimination processes in cyclic alcohols have demonstrated in the simple case of cyclohexanol that loss of water occurs by a stereospecific 1,4-*cis*-elimination (43% *cis*-4*H*) without ring cleavage and by a set of nonstereospecific reactions involving ring cleavage prior to dehydration when participation of the C-3 (C-5) hydrogens is predominant.[7,8,9]

The reason why a *cis*-1,4- and not a *cis*-1,3-elimination is allowed, has been interpreted as being associated with the different minimum distances which can be achieved without ring cleavage between the hydroxyl oxygen and the *cis*-4- and *cis*-3-hydrogens, respectively, cf. Scheme 1. Only in the former case is the value below 1·8 Å regarded as the maximum distance for bond formation.[8]

While such a maximum distance seems applicable when a secondary non-activated hydrogen is involved, it appears not to be a fixed parameter, but rather a function of the dissociation energy of the hydrogen involved. Evidence in favour of this has been given by Karliner *et al.*,[10] who have shown by deuterium labelling that elimination of water from the [M − 15] ion derived from cholestan-3α-ol (I) involves mainly the 5α-hydrogen (70 to 75%), while the corresponding reaction in the 3β-epimer is quite unspecific. Similarly, results recently obtained in this laboratory† for 9α-*d*-podocarpan-12α-ol (II) and its 12β-hydroxy epimer show that loss of DHO occurs nearly exclusively in the 12α-hydroxy compound (60% DHO), which clearly suggests that dehydration by *cis*-1,3-elimination without ring cleavage is a dominating reaction when the hydrogen involved is tertiary. It has also recently been shown by deuterium

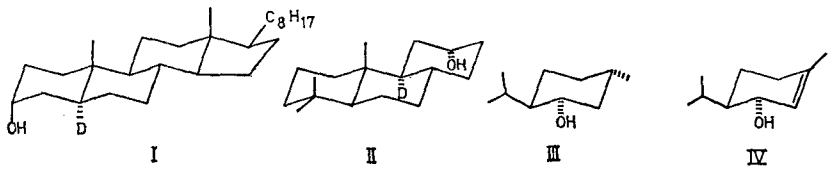
* $\Sigma_{40} I$ constitutes the sum of the relative intensities of all peaks above *m/e* 39. The relative intensities are then expressed as a percentage of the intensity of the strongest peak, which is assigned the value 100.

† C. R. Enzell and I. Wahlberg, unpublished results.




SCHEME 1. Conformations of cyclohexanols

labelling that loss of water occurs mainly by a 1,3-mechanism in *trans*-3-methylcyclohexanol but by a 1,4-mechanism in the corresponding *cis* derivative on photoionization.[11] Moreover, enhanced loss of DHO by *cis*-1,4-elimination is encountered when *cis*-4-*d*-cyclohexanol is substituted by an isopropyl group in the 4-position[12] and when a double bond is introduced in an allylic position to the carbon carrying the label under consideration, as demonstrated for the menthol (III)/*trans*-piperitol (IV) pair.[13,14]




Evidence from nonlabelled compounds has been given by Dolejš and Hanuš,[15] who have shown that *trans*-3- and *trans*-4-*tert*-butylcyclohexanol give higher $[M - 18]^{+\cdot}$ ($\% \sum_{24}$) and $[M - 18]^{+\cdot}/[M]^{+\cdot}$ values than the corresponding *cis* derivatives. This situation is also reported to persist in the corresponding 2-monomethyl and 2,2-dimethyl substituted epimeric pairs. It was concluded from these results that the ground state conformation seemed to be preserved in the ionized state. Similarly, results obtained by Green and co-workers[16] for 3- and 4-substituted cyclohexanols may also be quoted to support that 1,3-elimination can occur without ring cleavage. Thus, of the 1,3-disubstituted epimers the *trans* isomer eliminates water more readily than the *cis* isomer. This difference is enhanced when the bulkiness and stabilizing effect of the substituent R is increased, i.e. higher probability of the 3-H and 1-OH occupying axial positions, and minimum separation and increased stabilisation of a radical or cationic site at C-3. This can evidently only be accounted for if transannular 1,3-elimination occurs, since if ring cleavage dominated no major differences would be anticipated and if the 1,4-reaction dominated a reverse relationship would be expected on conformational grounds, i.e. water elimination by the 1,4-process would be favoured in the *cis* rather than in the *trans* epimer on account of the orientation favoured by R (cf. Scheme 1). It is also evident from the results of Dolejš and Hanuš[15] that the $[M - 18]^{+\cdot}$ values display less variation than the $[M - 18]^{+\cdot}/[M]^{+\cdot}$ values, and accordingly they are used here in preference to the latter.

Elimination by 1,3- and 1,4-processes is also possible in 2-alkylcyclohexanols when the substituent is isopropyl, as demonstrated by deuterium labelling in the case of

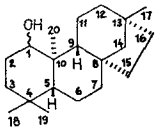
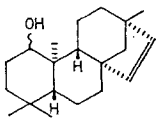
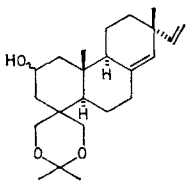
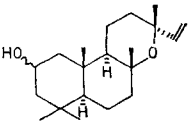
menthol (III). The hydrogen abstracted from carbon originates predominantly from the isopropyl side chain; about one quarter stems from the terminal carbons and about one half from the tertiary C-8, revealing that 1,3- and 1,4- eliminations from substituents on vicinal carbons are favoured processes when the adequate geometry can be achieved. Negligible transfer from C-2, C-4 and C-5 seems to indicate that the dehydration proceeds mainly without ring cleavage.[13]

In addition to the 1,3- and 1,4-elimination processes mentioned,* loss of water can also occur by a transannular 1,5-reaction when there is a hydrogen available on the α-carbon of the *cis* oriented 4-substituent. As shown by deuterium labelling, this reaction competes favourably with the 1,3-elimination. It is also nearly as favoured as the 1,4-elimination when the energy for removing the carbon bonded hydrogen is about the same.[12]

With this information about the simpler compounds at hand it is now worth turning to the discussion of the diterpene epimers, which due to their greater complexity, frequently offer new situations.

The structures of the diterpenoids incorporating a cyclohexanol moiety now examined are shown in Table 1 along with the intensity values ($I/\sum_{40} I$) of their

TABLE 1. INTENSITIES OF THE [M − 18] PEAKS, $I_{[M-18]}/\Sigma I$, IN THE SPECTRA OF THE EPIMERIC ALCOHOLS

| Compound | No. | Orientation of —OH | $I_{[M-18]}$ 70 eV | $I_{[M-18]}$ 10 eV |
|---|---|---|---|---|
|  | (1) | α | 3·69–4·13 | 8·33–8·63 |
| | (2) | β | 5·46–5·72 | 11·48–12·05 |
|  | (3)[c] | α | 1·74–1·90 | 3·32–3·45 |
| | (4)[d] | β | 1·67–1·76 | 3·61–3·73 |
|  | (5)[e] | α | 0·53–0·55 | 1·54–1·61 |
| | (6)[e] | β | 0·09–0·18 | 0·08–0·25 |
|  | (7) | α | 0·00–0·01 | 0·11–0·11 |
| | (8) | β | 0·00–0·02 | 0·00–0·00 |

* The extent to which simple 3-alkylcyclohexanols undergo dehydration by 1,4-elimination involving the hydrogen on the α-carbon of the substituent does not seem to have been directly established by deuterium labelling.

TABLE 1 (*continued*)

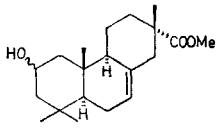
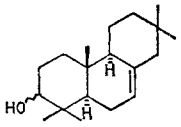
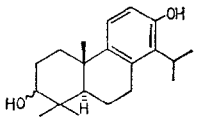
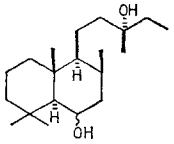
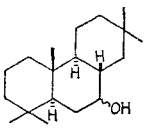
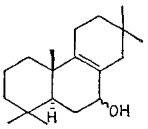
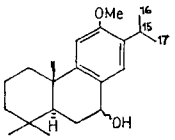
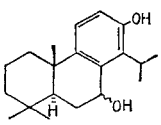
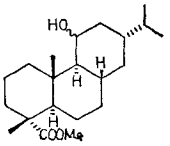
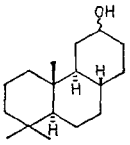
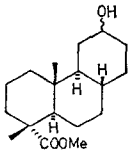
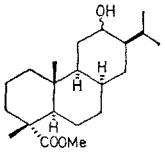
| Compound | No. | Orientation of —OH | $I_{[M-18]}$ 70 eV | $I_{[M-18]}$ 10 eV |
|---|---|---|---|---|
|  | (9) | α | 6·5[a] | |
| | (10) | β | 1·0 | |
|  | (11)[f] | α | 1·64–1·78 | 4·54–5·18 |
| | (12)[f] | β | 1·26–1·43 | 4·12–4·56 |
|  | (13)[g] | α | 0·00–0·03 | 0·17–0·21 |
| | (14)[g] | β | 0·00–0·03 | 0·01–0·17 |
|  | (15)[h] | α | 0·45–0·51 | 1·64–1·72 |
| | (16)[h] | β | 0·19–0·23 | 0·75–0·80 |
|  | (17)[f] | α | 2·58–3·08 | 10·84–11·26 |
| | (18)[f] | β | 0·94–1·09 | 3·68–3·80 |
|  | (19)[f] | α | 3·15–3·29 | 6·69–6·86 |
| | (20)[f] | β | 2·61–2·71 | 5·89–6·12 |
|  | (21) | α | 3·03–3·61 | 13·27–13·87 |
| | (22) | β | 2·51–2·78 | 11·39–11·60 |
|  | (23) | α | 2·67–3·19 | 15·09–16·95 |
| | (24) | β | 2·71–3·19 | 17·78–19·43 |

TABLE 1 (*continued*)

| Compound | No. | Orientation of —OH | $I_{[M-18]}$ 70 eV | $I_{[M-18]}$ 10 eV |
|---|---|---|---|---|
|  | (25)[i] | α | 2·34–2·41 | 6·37–6·54 |
| | (26)[i] | β | 3·27–3·47 | 7·75–8·04 |
|  | (27) | α | 3·55–3·72 | 7·38–7·54 |
| | (28) | β | 4·94–5·06 | 9·00–9·71 |
|  | (29) | α | 4·33–4·65 | 6·53–7·81 |
| | (30) | β | 2·27–2·54 | 4·94–5·67 |
|  | (31)[j] | α | 1·05–1·14 | 3·84–4·25 |
| | (32)[j] | β | 1·45–1·56 | 4·48–5·16 |

[a] These values are the average of three recordings undertaken on an earlier occasion and not repeated here due to the lack of material.

[b] The values obtained for the 1,1,2,3,3-$d_5$-derivatives of 7 and 8 (7a and 8a) agree with those obtained for the nonlabelled compounds. The same is true for the 3-$d_1$-derivatives of 11 and 12 (11a and 12a) and for the 6,6,7-$d_3$-derivatives of 23 and 24 (23a and 24a).

[c] Private communication from J. D. Connolly.

[d] Ref. 20.

[e] Ref. 21.

[f] Ref. 22.

[g] Ref. 23.

[h] Ref. 24.

[i] Ref. 25.

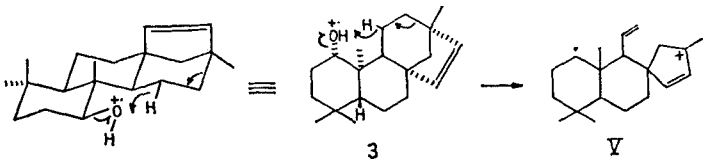
[j] Ref. 18

$[M - 18]^{+\cdot}$ peaks at 70 and 10 to 12 eV, given as intensity intervals at a 95% confidence level. These values reflect both the relative rates of formation and decomposition of the $[M - 18]^{+\cdot}$ species. However, on the basis of findings made to date, they seem adequate for the present purpose, since the relative rates of decomposition of the $[M - 18]^{+\cdot}$ species, as well as the course and rates of the other reactions, appear sufficiently similar in the two epimers when their spectra are similar. The observed intensity differences would then primarily correspond to the relative rates of formation of the $[M - 18]^{+\cdot}$ species from the molecular ion, which in turn reflect the difference in stereochemistry.

Of the 1-hydroxy diterpenoids (1 to 4), the first epimeric pair (1, 2) displays the expected differences. Thus, the β-epimer (2) which has the hydroxyl groups *cis* to the hydrogens on tertiary carbons (C-5 and C-9) for 1,3-elimination, exhibits a stronger

$[M - 18]^{+\cdot}$ peak than the α-isomer (1) having only secondary and hence energetically less available hydrogens in appropriate positions. Of the latter, only the 11β-hydrogen can be abstracted without a conformational change.

The results obtained for the second pair of 1-hydroxy epimers (3, 4) at 70 eV initially appear anomalous on the basis of the findings for the first pair (1, 2). However, inspection of Dreiding models shows that in the α-isomer (3) the 11β-hydrogen is not only situated close to the hydroxyl oxygen (1·7 Å) as in the epimer 1, but the bond between the 11β-hydrogen and C-11 is *trans* relative to the allylic 12,13-bond. The geometry therefore is ideally disposed for a concerted reaction involving cleavage of these bonds and formation of a bond between the hydroxyl oxygen and the 11β-hydrogen, and hence for the generation of an allylically stabilised $[M - 18]^{+\cdot}$ species (V) (Scheme 2). Thus, the 11β-hydrogen may be regarded as 'pseudo-allylically



3 V

SCHEME 2

activated' and its bond dissociation energy of the same order as that of a non-activated hydrogen attached to a tertiary carbon. Support for the formulation of the $[M - 18]^{+\cdot}$ species (V), which also can be further stabilised by rupture of the 9,10-bond, comes from its subsequent fragmentation discussed below.

It is evident from the results obtained for the 2-hydroxy epimers (5 to 10) that loss of water occurs preferentially from the α-isomer. This is in agreement with expectation, since the hydroxyl group in this epimer is *cis* to the hydrogen at the tertiary C-5 and because there are no ring hydrogens available for water elimination in the β-epimers without carbon–carbon bond cleavage. Examination of Dreiding models clearly suggests that 1,5-elimination without ring cleavage is excluded in the case of the β-epimer because of the rigidity of the tricyclic structure. It also implies that the 9α-hydrogen cannot be utilised for water elimination in the 2α-epimer because the distance is too great. The lack of difference between the values obtained at 70 eV for the epimeric pair 7 and 8, and probably also for the epimers 13 and 14, is not due to thermal dehydration prior to ionisation, as demonstrated by the absence of 1,2-elimination in the corresponding 1,1,2,3,3-$d_5$-derivatives (7a, 8a), but clearly to the occurrence of other more highly favoured fragmentation reactions. In such cases, when 10 eV results are not confirmed by 70 eV measurements, relevant peaks at lower mass numbers displaying intensity differences may frequently be used to provide supporting evidence (*vide infra*).

The situation in the 3-hydroxy compounds (11 to 14) is much the same as in the 2-hydroxy derivatives, since only with the α-isomers, which show the higher $[M - 18]^{+\cdot}$ peaks, are there hydrogens on tertiary carbons in appropriate positions.

The α-epimer of the 6-hydroxy compounds (15, 16) also exhibits the stronger $[M - 18]^{+\cdot}$ peak, as predicted from the availability of hydrogens on tertiary carbons for 1,3- and 1,4-eliminations in this but not in the β-epimer. Although 1,5-elimination involving a hydrogen at C-11 seems possible in the latter compound, it should be less

favoured than the 1,4-elimination in the α-isomer for reasons detailed above. It is probably also even less favoured than the 1,3-elimination in the α-isomer, since the *trans* fusion to ring A reduces the flexibility of ring B and hence increases the energy requirement for the bond forming process in the 1,5-elimination. This decrease in flexibility evidently also makes the 1,4-elimination less favoured in the α-isomer (16) than in cyclohexanol.

Of the 7-hydroxy compounds, the epimers 17 to 22 conform to the regular pattern, since elimination of water by a 1,3-process involving hydrogens on tertiary carbon, 5α-H (in 18 also 9α-H), should be favoured over a 1,5-elimination involving hydrogens on a primary carbon (20-H). In the epimeric pair 19 and 20 participation of the allylic hydrogens in *peri* position seems feasible, but, judging from Dreiding models, their contribution would be about the same in both epimers. The remaining pair of 7-hydroxy epimers (23, 24) gives values at 70 eV which are virtually identical, while the values obtained at 10 eV favour the β-isomer. In this case, however, the uncertainty is not due to low intensity, nor does thermal dehydration appear to be an important factor, since loss of HDO in the corresponding 6,6,7-$d_3$-derivatives (23a, 24a) does not exceed 20% of the total water loss. The intensity values obtained for the deuterated compounds also confirm that water elimination is favoured in the case of the β-epimer. It may be concluded therefore, that competition between the hydrogen at C-5 and those on the angular methyl group at C-10, which would have favoured the α-epimer strongly, is virtually without significance, since the benzylic hydrogen on the isopropyl group can be utilised in both isomers and this is an energetically favoured process. Therefore, the observed intensity differences in this case may be better explained by the fact that in the ground state the hydroxyl group in the β-isomer is equatorially oriented and close to the 17-hydrogen, while in the α-isomer it is axial and more remote from this 17-hydrogen. Elimination of water from the latter isomer therefore requires a conformational change, a reaction which when compared to that of the β-isomer is likely to have a lower rate constant.

The β-epimer of the 11-hydroxy compounds (25, 26) exhibits the stronger $[M - 18]^{+\cdot}$ peak, which is in agreement with expectation, since only in this isomer are there hydrogens on tertiary carbons in appropriate positions for elimination of water.* While both isomers have secondary hydrogens in positions allowing transannular 1,4-eliminations the rigidity of the cyclic system is likely to reduce the importance of these reactions. It should be noted that elimination of water through loss of the 1β-hydrogen obviously also occurs in the α-isomer; the distance is about 1·5 Å and such a reaction has been encountered previously in steroids[17] (*vide infra*). As may be expected, however, the abundance of the resulting ion is lower than that of the $[M - 18]^{+\cdot}$ species derived from the β-isomer, since the 1β-hydrogen is on a secondary carbon while the 8β- and 13β-hydrogens are attached to tertiary carbons. Moreover, further fragmentation of the $[M - 18]^{+\cdot}$ species derived through loss of the 1β-hydrogen is probably favoured as opening of ring B obviously occurs simultaneously.

The results obtained for the three pairs of 12-hydroxy epimers (27 to 32) are consistent with predictions for only one of these (27, 28), while for the other two (29 to 32) they appear anomalous in the sense that the isomers 29 and 32 having the hydroxyl group *cis* to the hydrogen at the tertiary C-8 exhibit lower values. However,

* A further possibility exists in the α-isomer when the hydroxyl and isopropyl groups are axial in a ring C boat conformer.

the differences between the epimers in each of these pairs, with respect to the steric and energetic situation for dehydration, are small and less clearly distinguishable than for the previously discussed compounds.

The 12-hydroxy epimers 31 and 32 have rings B and C *cis* fused and possess, according to published chemical and n.m.r. data, all chair conformations in which the ring C chair is somewhat distorted.[18] It is evident from these results and from inspection of Dreiding models, that the hydroxyl group in the $\beta$-isomer is very close to the hydrogens of the angular methyl group and that twisting of ring C, eliminating excessive repulsive forces between these two groups, brings the hydroxyl group closer to the tertiary 15-hydrogen of the isopropyl group (minimum distance in eclipsed conformation 1·7 Å). As discussed above for menthol[13] this is a favoured reaction and the energy required would be lower when the hydroxyl and isopropyl groups are *cis*, since the transition state involving a *cis* fused 5-membered ring should be of lower energy here than one involving a corresponding *trans* fused moiety.[8]

As mentioned in the preceding section, the intensities of the $[M - 18]^{+\cdot}$ peaks were in two cases too low at 70 eV to provide support for the results obtained at 10 eV. Such support may, however, often be obtained from other parts of the spectra and three principally different alternatives may be considered:

(1) When fragment ions $[M - X]^+$ formed by identical paths are encountered, in which essentially the same steric situations with respect to the dehydration processes persist, the ions resulting on dehydration of these giving $[M - X - 18]^+$ ions may convey the same information regarding the steric relationships in the epimeric pair as the $[M - 18]^{+\cdot}$ ions.

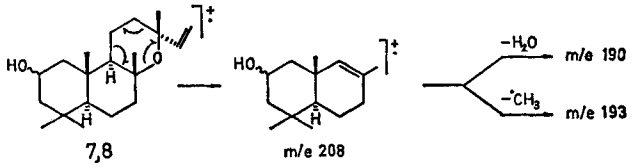
(2) Localisation of the charge to the hydroxyl oxygen also causes reactions initiated by cleavage of the carbon–carbon bonds extending from the asymmetric hydroxylated carbon ($\alpha$-cleavage) which compete with dehydration. The outcome of this competition is frequently different in the two epimers. The main reason is that the stereochemical effect on the rate constants for the $\alpha$-cleavage reaction, mainly governed by the enthalpy discrepancy, is usually small relative to that on the rate constants for the dehydration, since the bond forming process often is rate determining. As a consequence of the larger difference between the rate constants for dehydration in the two epimers, reactions initiated by the competing $\alpha$-cleavage will be of proportionately greater importance in the less readily dehydrated epimer and *vice versa.*

(3) When different hydrogens are utilised in the dehydration of the two epimers, this sometimes influences the fragmentation pattern considerably, since certain subsequent or simultaneous reactions giving $[M - 18 - X]^+$ ions occur, or are highly favoured, in only one of the epimers. Therefore, when such product ions $[M - 18 - X]^+$ are of high stability, the spectra of the two epimers may be quite different and some of the pronounced spectral differences correlated with the stereochemical differences. Some illustrations of such reactions are given below. They may, of course, also be useful as corroborative evidence when there are pronounced differences between the $[M - 18]^{+\cdot}$ values at 70 eV.

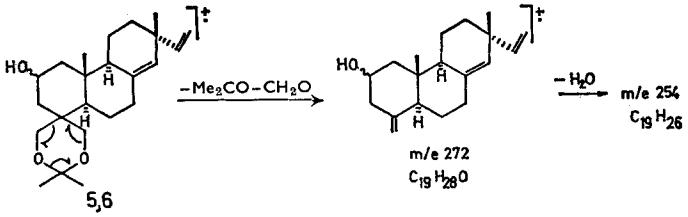
In the case of the 2-hydroxymanoyl oxide epimers (7, 8), which display $[M - 18]^{+\cdot}$ peaks of inadequate intensity, the elimination of the tetrahydropyran ring is a highly favoured reaction giving rise to a prominent fragment of *m/e* 208 (cf. Scheme 3).[19] The steric requirements and the activation energy for this reaction should be about

the same in both isomers, while, in contrast, subsequent elimination of water should be clearly favoured for the α-isomer, where the tertiary α-oriented hydrogen at C-5 is located within bond forming distance. Consistent with this, the resulting *m/e* 190 ion is almost three times as abundant for this isomer as for the β-isomer, whereas the abundances of the parent *m/e* 208 ions and also of the *m/e* 193 ions, which are derived from *m/e* 208 species by loss of the angular methyl group, are roughly the reverse. Similarly, dehydration of the *m/e* 207 ion is more favoured when derived from the α-isomer than from the β-isomer.

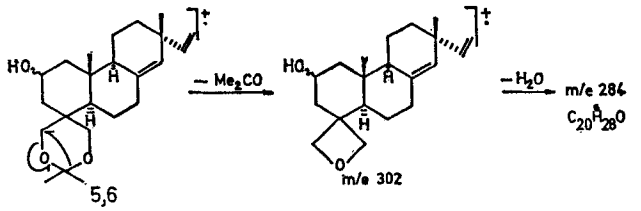
A further example of such a $[M - X]^{+\cdot} \rightarrow [M - X - H_2O]^{+\cdot}$ reaction is encountered in the spectra of the epimers 5 and 6, in which the ions of *m/e* 272 and 302 may be formulated as indicated below (Scheme 3). The dehydration of these ions, in which the steric relationships between the hydroxyls and 5α-hydrogens are preserved,




| | $I_{208}$ | | $I_{193}$ | | $I_{190}$ | |
|---|---|---|---|---|---|---|
| | 70 eV | 10 eV | 70 eV | 10 eV | 70 eV | 10 eV |
| (7) α | 0·71–0·74 | 2·15–2·26 | 0·47–0·49 | 0·92–0·95 | 2·25–2·41 | 4·44–4·56 |
| (8) β | 1·38–1·52 | 4·50–4·66 | 0·80–0·90 | 1·71–1·78 | 0·68–0·78 | 1·81–1·86 |




| | $I_{272}$ | | $I_{254}$ | |
|---|---|---|---|---|
| | 70 eV | 10 eV | 70 eV | 10 eV |
| (5) α | 0·85–0·88 | 2·38–2·47 | 1·00–1·04 | 2·59–2·72 |
| (6) β | 1·67–1·71 | 3·95–4·40 | 0·80–0·82 | 2·45–2·60 |




| | $I_{302}$ | | $I_{284}$ | |
|---|---|---|---|---|
| | 70 eV | 10 eV | 70 eV | 10 eV |
| (5) α | 0·21–0·24 | 0·62–0·68 | 0·58–0·61 | 1·68–1·77 |
| (6) β | 0·40–0·42 | 0·90–1·23 | 0·39–0·41 | 1·10–1·15 |

SCHEME 3. Examples of the $[M - X]^{+\cdot} \rightarrow [M - X - H_2O]^{+\cdot}$ type of fragmentation.

is clearly favoured in the case of the α-isomer, as demonstrated by the higher abundances of the dehydrated ions (*m/e* 254 and 284) in this isomer despite the lower abundances of their parents (*m/e* 272 and 302).

Pertinent examples demonstrating that ions formed by reactions initiated by α-cleavage are more abundant in the case of the less readily dehydrated epimer are encountered for several epimeric pairs, e.g. the formation of the *m/e* 153 and 124 ions from the 6-hydroxy epimers (15, 16), and the *m/e* 139 and 140 ions from the 7-hydroxy epimers (17, 18, Fig. 1). The formation of these ions may be depicted as shown in Scheme 4.

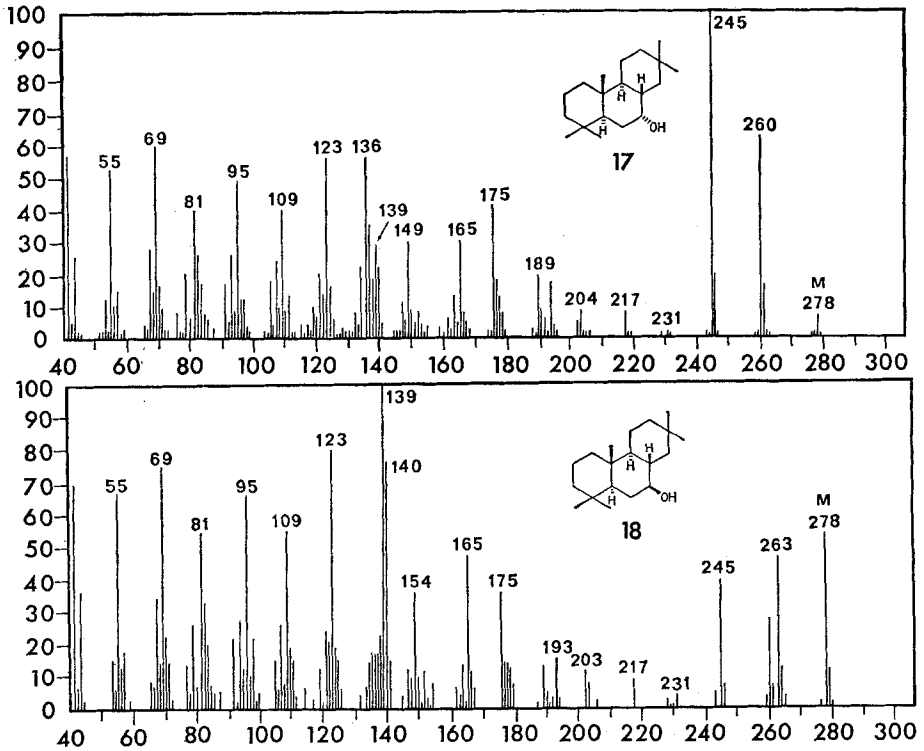
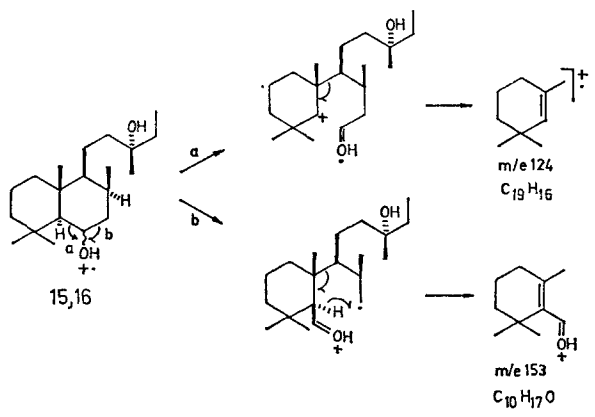
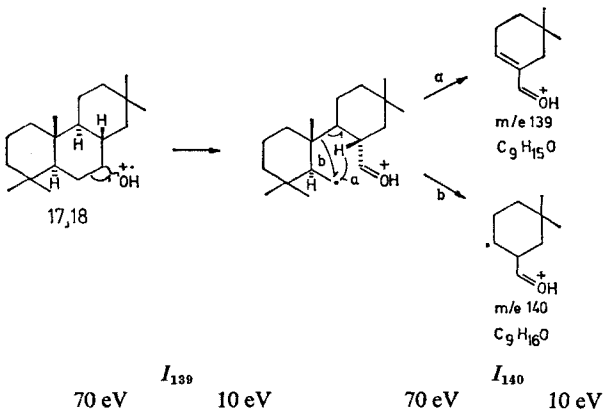



FIG. 1. Mass spectra of 16-norpimaran-7α-ol (17) and 16-norpimaran-7β-ol (18).

The third possibility of obtaining stereochemical information from the lower part of the spectra, which is based on the fact that the elimination of different hydrogens in an epimeric pair on dehydration may significantly influence subsequent or simultaneous reactions giving rise to $[M - 18 - X]^+$ ions, is frequently encountered and is here illustrated by five examples. Of the 3-hydroxy compounds 13 and 14, which could not be distinguished by the $[M - 18]^{+\cdot}$ peaks at 70 eV, the α-epimer gives a much stronger $[M - 33]^+$ peak. This can be ascribed to the fact that only this isomer can undergo the reaction outlined in Scheme 5, which gives rise to a highly stabilised $[M - 33]^+$ species. The importance of this reaction is also well illustrated by the large differences in $\sum_{40} I$ values. Similar situations are encountered for the 7-hydroxy compounds 17 and 18 (cf. Fig. 1), the 11-hydroxy derivatives 25 and 26 and the 12-hydroxy isomers 31 and 32, in which the further fragmentation of the $[M - 18]^{+\cdot}$ ions




| | $I_{124}$ | | $I_{153}$ | |
|---|---|---|---|---|
| | 70 eV | 10 eV | 70 eV | 10 eV |
| (15) α | 1·06–1·12 | 1·56–1·61 | 2·61–2·83 | 5·49–5·58 |
| (16) β | 1·35–1·43 | 2·46–2·65 | 4·44–4·83 | 7·41–7·96 |



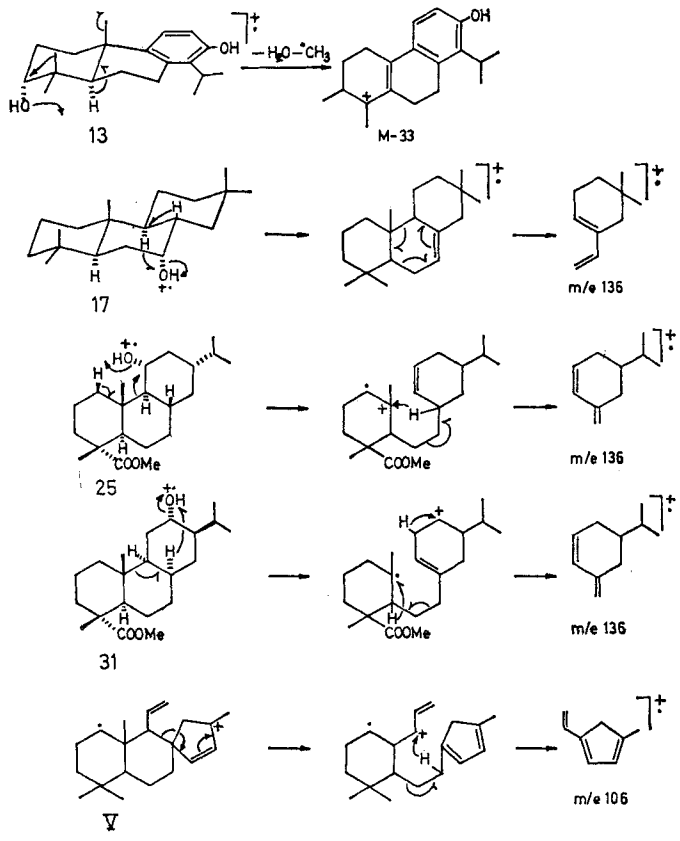

| | $I_{139}$ | | $I_{140}$ | |
|---|---|---|---|---|
| | 70 eV | 10 eV | 70 eV | 10 eV |
| (14) α | 1·36–1·56 | 3·03–3·24 | 1·10–1·27 | 2·81–3·04 |
| (18) β | 4·97–5·27 | 11·02–13·48 | 3·66–3·90 | 9·89–12·09 |

SCHEME 4. Examples of fragmentation reactions involving α-cleavage.

derived from the α-epimers occurs readily giving $C_{10}H_{16}$ (h.r.) species of *m/e* 136 comprising ring C. In the case of the 1-hydroxy epimers 3 and 4, the further fragmentation of the intermediate (V) derived from the α-isomer gives a prominent *m/e* 106 species (Scheme 5). The absence of this fragmentation in the corresponding dihydro-derivative (1), further supports this formulation.

*Epimers differing at ring junctions*

Previous studies have shown that compounds epimeric with respect to ring fusion, notably A/B *cis* and *trans* fused steroids, usually display small spectral differences when the enthalpy difference is the only factor of importance. A common observation in such cases is that the epimer of lower enthalpy exhibits the stronger molecular peak.[1,4,26,27,28] This situation, which ideally applies to saturated hydrocarbons, may




| | $\Sigma I$ | | | $I_{[M-33]}$ | |
|---|---|---|---|---|---|
| | 70 eV | 10 eV | | 70 eV | 10 eV |
| (13) α | 455–474 | 307–313 | (13) α | 21·06–22·01 | 31·95–32·62 |
| (14) β | 252–1550 | 379–444 | (14) β | 5·29–6·51 | 10·71–11·62 |

| | $I_{136}$ | | | $I_{136}$ | |
|---|---|---|---|---|---|
| | 70 eV | 10 eV | | 70 eV | 10 eV |
| (17) α | 3·22–3·45 | 8·60–9·09 | (25) α | 4·40–4·69 | 3·69–4·25 |
| (18) β | 0·86–0·95 | 1·73–1·85 | (26) β | 1·01–1·07 | 1·65–1·71 |

| | $I_{136}$ | | | $I_{106}$ | |
|---|---|---|---|---|---|
| | 70 eV | 10 eV | | 70 eV | 10 eV |
| (31) α | 8·77–9·17 | 19·16–23·49 | (3) α | 3·56–3·80 | 4·87–5·08 |
| (32) β | 2·61–2·83 | 6·37–7·13 | (4) β | 1·79–1·93 | 1·49–1·62 |

SCHEME 5. Examples of the $[M - H_2O]^{+\cdot} \rightarrow [M - H_2O - X]^+$ type of fragmentation.

be drastically altered in hetero atom containing compounds, since on account of the different geometry the hetero atom may be located within bond forming distance of certain hydrogens in only one of the epimers, thus triggering additional fragmentation reactions. The relative stability of the molecular ion is thereby affected and simultaneously considerable spectral differences between the epimers are generally observed.[3,27,29,30] In fact, such bond forming reactions may also be of critical importance in hydrocarbons as recently demonstrated by Tökés and Amos for C-17 side

chain containing steroids, which exhibit stereospecific fragmentation reactions diagnostic for the configuration at C-5.[31]

An examination of the nine pairs of epimers 33 to 50, detailed in Table 2, is consistent with these views. All the epimeric pairs examined, with the exception of 37 and 38, conform to the simple pattern predictable on the basis of the enthalpy differences, i.e. the more stable *trans* fused isomer shows the higher molecular peak. The reason for observing the reverse relationship for the epimeric pair 37 and 38 is clearly due to the fact that in the *trans*-A/B isomer (37), but not in the *cis*-A/B isomer (38), the hydroxyl group is situated very close to the tertiary benzylic hydrogen. This enables the formation of abundant $[M - 18]^{+\cdot}$, $[M - 18 - 15]^{+}$ and $[M - 18 - 29]^{+}$ ions (Scheme 6, Table 3), which occurs at the expense of other reactions, e.g. $[M]^{+\cdot} \rightarrow [M - CH_2OH]^{+}$ and reduces the stability of the molecular ion.

TABLE 2. TOTAL ION INTENSITIES $\Sigma I$ AND INTENSITIES OF THE MOLECULAR PEAKS, $I_M/\Sigma I$ IN THE SPECTRA OF COMPOUNDS EPIMERIC AT RING JUNCTIONS

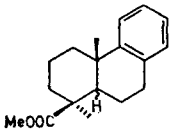
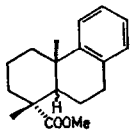
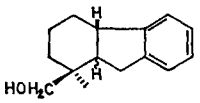
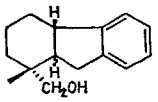
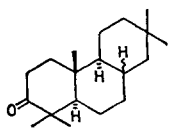
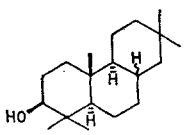
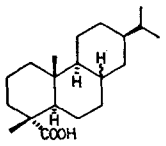
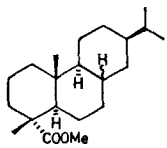
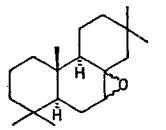
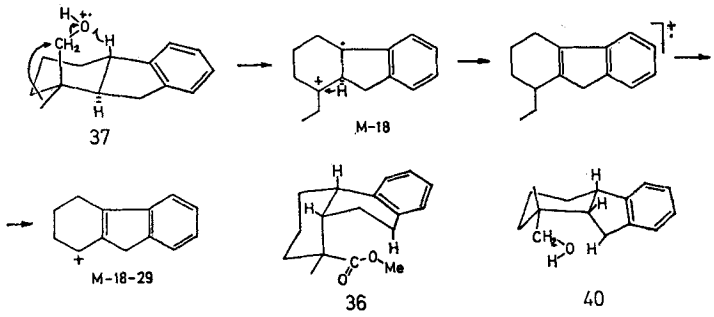
| Compound | No. | Orientation | 70 eV $I_M$ | 70 eV $\Sigma I$ | 10 eV $I_M$ | 10 eV $\Sigma I$ |
|---|---|---|---|---|---|---|
|  | (33)[a] | α | 2·30–2·39 | 546–603 | 9·10–10·28 | 297–356 |
| | (34)[a] | β | 0·51–0·71 | 1942–2164 | 4·09–5·70 | 719–913 |
|  | (35)[a] | α | 3·37–3·77 | 498–563 | 13·67–15·19 | 359–412 |
| | (36)[a] | β | 0·35–0·40 | 863–916 | 1·97–2·31 | 408–454 |
|  | (37)[b] | α | 3·39–3·63 | 1402–1504 | 13·88–15·24 | 658–720 |
| | (38)[b] | β | 4·33–4·91 | 903–947 | 18·50–19·82 | 380–405 |
|  | (39)[b] | α | 4·98–5·38 | 776–875 | 20·04–23·16 | 347–367 |
| | (40)[b] | β | 3·00–3·23 | 1509–1625 | 13·49–14·40 | 694–740 |
|  | (41)[c] | α | 2·30–2·55 | 896–1095 | 8·01–8·50 | 412–440 |
| | (42)[c] | β | 2·83–3·15 | 786–873 | 8·59–9·30 | 430–466 |
|  | (43)[c] | α | 0·70–0·99 | 1166–1374 | 1·40–1·46 | 543–568 |
| | (44)[c] | β | 1·58–1·80 | 2433–2585 | 2·58–2·82 | 1439–1504 |

TABLE 2 (*continued*)

| Compound | No. | Orientation | 70 eV $I_M$ | 70 eV $\Sigma I$ | 10 eV $I_M$ | 10 eV $\Sigma I$ |
|---|---|---|---|---|---|---|
|  | (45)[d] | α | 0·93–1·05 | 1023–1189 | 1·98–2·14 | 470–494 |
| | (46)[d] | β | 1·18–1·31 | 523–640 | 2·89–3·18 | 297–316 |
|  | (47)[d] | α | 1·46–1·50 | 964–1009 | 2·23–2·48 | 511–542 |
| | (48)[d] | β | 1·71–1·79 | 623–655 | 2·96–3·29 | 367–392 |
|  | (49)[c] | α | 1·45–1·56 | 1685–1707 | 4·35–4·92 | 997–1075 |
| | (50)[c] | β | 1·73–2·09 | 1612–1674 | 4·94–5·81 | 879–949 |

[a] Ref. 32.
[b] Private communication from U. R. Ghatak.
[c] Ref. 22.
[d] Ref. 33.

Analogous situations are encountered with the epimeric pairs 35, 36 and 39, 40. The proximity of the carbomethoxy group to the benzylic 7α-hydrogen in the 5β-isomer (36) of the former pair strongly favours the formation of well stabilized $[M - 32]^{+\cdot}$ and $[M - 60]^{+\cdot}$ ions. Similarly, the proximity of the carbinol group to the benzylic methylene hydrogens in the β-isomer (40) of the latter pair allows the generation of very abundant $[M - 18]^{+\cdot}$, $[M - 18 - 15]^{+}$ and $[M - 18 - 29]^{+}$ ions (Scheme 6, Table 3). The presence of these additional fragmentation reactions in 36 and 40 necessarily also leads to decreased abundances of the molecular ions. Here, however, these reactions occur in the epimers having the lower enthalpies and hence do not reverse but reinforce the intensity differences expected in view of the different enthalpies.




SCHEME 6

TABLE 3. INTENSITIES, $I/\Sigma I$, OF THE [M − 18], [M − 18 − 15] AND [M − 18 − 29] PEAKS IN THE SPECTRA OF 37, 38, 39 AND 40

| | $I_{[M-18]}$ | | $I_{[M-18-15]}$ | | $I_{[M-18-29]}$ | |
|---|---|---|---|---|---|---|
| | 70 eV | 10 eV | 70 eV | 10 eV | 70 eV | 10 eV |
| (37) | 1·92–2·04 | 5·50–6·58 | 3·21–3·36 | 6·34–7·09 | 5·04–5·35 | 8·96–9·60 |
| (38) | 1·20–1·32 | 4·22–4·79 | 2·59–2·81 | 5·31–6·03 | 2·56–2·65 | 4·70–4·85 |
| (39) | 0·34–0·37 | 1·10–1·22 | 1·40–1·52 | 2·71–3·03 | 2·07–2·24 | 3·39–3·77 |
| (40) | 1·42–1·53 | 5·00–5·85 | 3·99–4·29 | 9·45–9·64 | 5·77–6·18 | 12·88–13·24 |

We also found the $\sum_{40} I$-values at 70 eV (cf. Table 2), with one readily explicable exception (43, 44), to follow a regular pattern, i.e. a lower value is registered for the epimer displaying the higher molecular peak.

*Epimers differing in the orientation of carbon–carbon linked substituents*

In contrast to the generally good stereochemical-spectral correlations observed for the two groups of epimers discussed above, the isomers (33 to 40, 46, 51 to 81), differing with respect to the orientation of carbon–carbon linked substituents (R) at C-4, C-12 or C-13, gave results that were fairly inconsistent when compared on the basis of the relative intensities of the $[M]^{+\cdot}$, $[M - 15]^+$ and $[M - R]^+$ peaks (Table 4). These observations accord well with the small enthalpy differences between epimers of this type which, in turn, lead to small and not readily recognised spectral differences. Similar results have previously been reported on several occasions,[1] e.g. for epimeric methyl decalins.[34] However, in a few cases, reactions involving bond forming processes are again more favoured in one of the epimers exclusively and result in considerable spectral differences.

Thus, due to the geometry of the A/B *cis* fused system, the equatorial carbomethoxy group in 36 and the equatorial carbinol group in 40 (Scheme 6), in contrast to their axial counterparts (34 and 38) are located close to benzylic hydrogens. This difference is revealed by more abundant $[M - 32]^{+\cdot}$ and $[M - 60]^{+\cdot}$ ions for the equatorial ester (36) and by more pronounced dehydration reactions in the equatorial carbinol derivative (40, *vide supra*, Table 3).

On the other hand, the geometry of the A/B *trans* fused system locates the axial carbinol group in 37 within bond forming distance of the tertiary benzylic hydrogen. Therefore, the fragmentation of 37 involves not only simple elimination of a carbinol radical to give a $[M - 31]^{+\cdot}$ species and subsequent decomposition of this to an ion of mass 129 as in 39, but also favoured dehydration reactions (Table 3).

The higher intensities of the $[M - 43]^+$ and *m/e* 159 peaks in the spectrum of the axial aldehyde (56) than of those in the spectrum of the equatorial epimer (55) are also explained by a stereospecific bond forming reaction. Thus, labelling studies, e.g. a 50% retention of the aldehydic hydrogen in the *m/e* 159 species, and observations of appropriate metastables have shown that the formation of the $[M - 43]^+$ and *m/e* 159 ions in 56 proceed not only via the decomposition reactions common to both epimers but also via an alternate route (Scheme 7). This route, which involves transfer of the aldehydic proton to C-10 in the [M − 15] ion as a crucial step, is less likely to be of importance in the equatorial epimer due to the greater distance.[35]

TABLE 4. INTENSITIES OF THE MOLECULAR $[M]^{+\cdot}$, $[M - 15]^{+}$ AND $[M - R]^{+}$ PEAKS, EXPRESSED AS A PERCENTAGE OF THE TOTAL ION INTENSITIES, IN THE SPECTRA OF COMPOUNDS DIFFERING IN THE ORIENTATION OF CARBON–CARBON LINKED SUBSTITUENTS

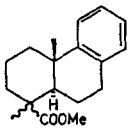
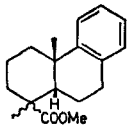
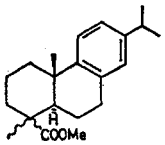
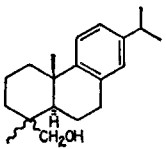
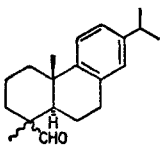
| Compound | No. | Orientation of R[a] | 70 eV $I_M$ | 70 eV $I_{[M-15]}$ | 70 eV $I_{[M-R]}$ | 10 eV $I_M$ | 10 eV $I_{[M-15]}$ | 10 eV $I_{[M-R]}$ |
|---|---|---|---|---|---|---|---|---|
|  | (35)[c] | α | 3·37–3·77 | 3·83–4·47 | 0·90–0·99 | 13·67–15·19 | 11·91–16·44 | 1·77–2·13 |
| | (33)[c] | β | 2·30–2·39 | 5·55–5·74 | 0·77–0·80 | 9·10–10·28 | 11·61–13·21 | 1·19–1·36 |
|  | (36)[c] | α | 0·35–0·40 | —[b] | 1·13–1·24 | 1·97–2·31 | —[b] | 2·90–3·37 |
| | (34)[c] | β | 0·51–0·71 | 1·17–1·46 | 0·18–0·21 | 4·09–5·70 | 8·45–11·19 | 0·58–0·84 |
|  | (51)[d] | α | 3·02–3·52 | 3·61–4·14 | 0·83–0·89 | 15·60–18·37 | 14·45–16·73 | 1·78–1·88 |
| | (52)[d] | β | 3·86–4·15 | 8·70–10·18 | 0·86–0·92 | 17·73–19·56 | 29·00–32·48 | 1·52–1·76 |
|  | (53)[d] | α | 3·61–3·70 | 9·34–9·69 | 1·00–1·03 | 9·08–9·49 | 20·87–21·27 | 1·30–1·49 |
| | (54)[d] | β | 3·55–3·71 | 9·05–9·54 | 1·07–1·15 | 9·66–10·69 | 20·23–20·92 | 1·45–1·69 |
|  | (55)[d] | α | 4·17–4·28 | 6·79–6·94 | 0·78–0·80 | 16·69–18·54 | 17·46–19·00 | 1·81–1·93 |
| | (56)[d] | β | 3·06–3·73 | 1·50–1·65 | 0·58–0·62 | 12·57–15·86 | 4·41–5·21 | 1·44–1·64 |

TABLE 4 (*continued*)

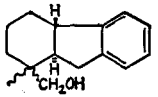
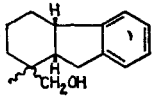
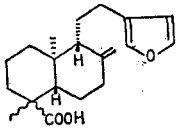
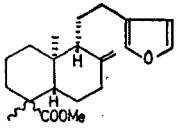
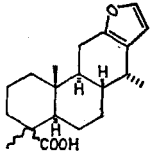
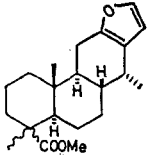
| Compound | No. | Orientation of R[a] | 70 eV $I_M$ | 70 eV $I_{[M-15]}$ | 70 eV $I_{[M-R]}$ | 10 eV $I_M$ | 10 eV $I_{[M-15]}$ | 10 eV $I_{[M-R]}$ |
|---|---|---|---|---|---|---|---|---|
|  | (39)[e] | α | 4·98–5·38 | 0·00–0·00 | 11·19–12·09 | 20·04–23·16 | 0·00–0·00 | 27·30–28·83 |
| | (37)[e] | β | 3·39–3·63 | 0·00–0·00 | 5·97–6·38 | 13·88–15·24 | 0·00–0·00 | 13·52–14·51 |
|  | (40)[e] | α | 3·00–3·23 | 0·00–0·00 | 3·80–4·10 | 13·49–14·40 | 0·00–0·00 | 9·07–9·42 |
| | (38)[e] | β | 4·33–4·91 | 0·00–0·00 | 10·57–11·09 | 18·50–19·82 | 0·00–0·00 | 24·64–26·46 |
|  | (57)[f] | α | 3·24–3·37 | 0·21–0·23 | 0·19–0·22 | 2·52–2·84 | 0·25–0·31 | 0·40–0·43 |
| | (58)[g] | β | 2·45–2·64 | 0·31–0·33 | 0·30–0·32 | 2·04–3·42 | 0·37–0·46 | 0·56–0·74 |
|  | (59)[f] | α | 2·52–2·86 | 0·17–0·20 | 0·89–1·02 | 9·49–12·25 | 0·67–0·73 | 2·23–2·47 |
| | (60)[g] | β | 2·12–2·29 | 0·23–0·26 | 1·05–1·13 | 8·51–9·13 | 0·80–1·13 | 2·39–2·68 |
|  | (61)[h] | α | 5·69–6·16 | 1·33–2·02 | 0·15–0·19 | 26·24–30·62 | 4·65–5·52 | 0·31–0·43 |
| | (62)[i] | β | 8·06–8·63 | 1·70–1·79 | 0·14–0·15 | 28·83–32·81 | 3·63–4·35 | 0·23–0·27 |
|  | (63)[h] | α | 7·91–8·98 | 0·68–0·77 | 1·06–1·16 | 30·65–32·70 | 1·72–1·93 | 1·90–2·12 |
| | (64)[i] | β | 7·62–8·18 | 0·85–0·92 | 1·01–1·08 | 30·79–32·44 | 2·16–2·51 | 1·78–2·03 |

TABLE 4 (*continued*)

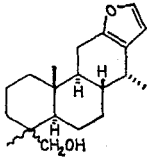
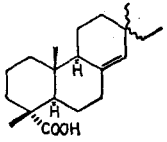
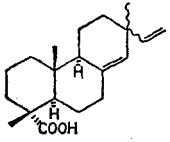
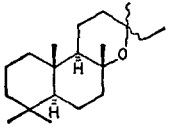
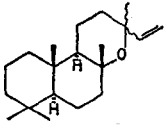
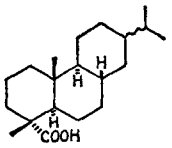
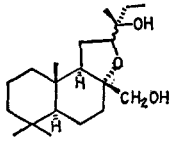
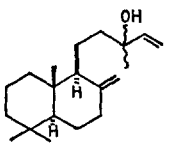
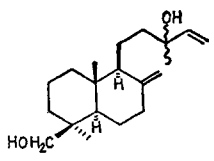
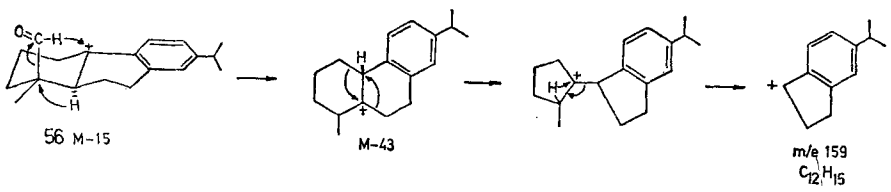
| Compound | No. | Orientation of R[a] | 70 eV $I_M$ | 70 eV $I_{[M-15]}$ | 70 eV $I_{[M-R]}$ | 10 eV $I_M$ | 10 eV $I_{[M-15]}$ | 10 eV $I_{[M-R]}$ |
|---|---|---|---|---|---|---|---|---|
|  | (65)[h] | α | 5·88–6·32 | 0·60–0·64 | 3·57–3·96 | 23·24–23·80 | 1·56–1·71 | 9·46–10·21 |
| | (66)[i] | β | 7·22–8·38 | 0·64–0·74 | 1·38–1·61 | 26·52–27·33 | 1·74–1·92 | 3·52–3·93 |
|  | (67)[j] | α | 0·33–0·37 | 0·60–0·66 | 9·60–10·53 | 1·11–1·62 | 1·56–2·13 | 29·87–35·82 |
| | (68)[j] | β | 0·25–0·38 | 0·47–0·65 | 7·84–10·46 | 1·15–1·51 | 1·18–1·75 | 29·04–32·09 |
|  | (69)[j] | α | 2·50–2·63 | 4·18–4·31 | 0·21–0·25 | 8·04–9·15 | 10·06–11·53 | 0·86–1·09 |
| | (70)[j] | β | 2·16–2·32 | 3·05–3·24 | 0·11–0·17 | 6·75–6·92 | 7·77–7·95 | 0·38–0·43 |
|  | (71)[k] | α | 0·00–0·00 | 1·15–1·22 | 2·48–2·63 | 0·00–0·00 | 3·14–3·37 | 8·07–8·77 |
| | (72)[l] | β | 0·00–0·00 | 0·83–0·95 | 2·64–2·95 | 0·00–0·00 | 2·22–2·71 | 7·19–7·97 |
|  | (73)[k] | α | 0·03–0·05 | 4·27–4·75 | 0·09–0·12 | 0·13–0·15 | 12·53–13·99 | 0·26–0·29 |
| | (74)[l] | β | 0·03–0·05 | 4·89–5·10 | 0·13–0·14 | 0·15–0·16 | 15·43–17·07 | 0·37–0·39 |

TABLE 4 (*continued*)

| Compound | No. | Orientation of R[a] | 70 eV $I_M$ | 70 eV $I_{[M-15]}$ | 70 eV $I_{[M-R]}$ | 10 eV $I_M$ | 10 eV $I_{[M-15]}$ | 10 eV $I_{[M-R]}$ |
|---|---|---|---|---|---|---|---|---|
|  | (75)[m] | α | 1·47–1·66 | 0·24–0·26 | 0·96–1·01 | 4·91–5·04 | 0·52–0·53 | 1·85–1·89 |
| | (46)[m] | β | 1·18–1·31 | 0·18–0·19 | 1·16–1·23 | 2·89–3·18 | 0·29–0·32 | 2·19–2·52 |
|  | (76)[n] | α | 0·00–0·00 | 0·00–0·00 | 0·38–0·42 | 0·00–0·00 | 0·00–0·00 | 1·37–1·40 |
| | (77)[n] | β | 0·00–0·00 | 0·00–0·00 | 0·06–0·08 | 0·00–0·00 | 0·00–0·00 | 0·20–0·21 |
|  | (78)[o] | α | 0·03–0·05 | 0·14–0·18 | 0·00–0·00 | 0·15–0·17 | 0·55–0·58 | 0·00–0·00 |
| | (79)[p] | β | 0·01–0·02 | 0·10–0·11 | 0·00–0·00 | 0·07–0·08 | 0·30–0·32 | 0·00–0·00 |
|  | (80)[q] | α | 0·00–0·02 | 0·02–0·08 | 0·00–0·00 | 0·00–0·00 | 0·00–0·00 | 0·00–0·00 |
| | (81)[p] | β | 0·00–0·00 | 0·00–0·00 | 0·00–0·00 | 0·00–0·04 | 0 02–0·10 | 0·00–0·00 |

[a] R = heavier substituent; [b] Exact values missing due to a technical error; [c] Ref. 32; [d] Ref. 35; [e] Private communication from U. R. Ghatak; [f] Ref. 36; [g] Ref. 37; [h] Ref. 38; [i] Ref. 39; [j] Ref. 40; [k] Ref. 2; [l] Ref. 41; [m] Ref. 33; [n] Ref. 42; [o] Ref. 43; [p] Ref. 44; [q] Ref. 45.




| | $I_{[M-43]}$ | | $I_{159}$ | |
|---|---|---|---|---|
| | 70 eV | 10 eV | 70 eV | 10 eV |
| (55) | 2·77–2·88 | 6·37–7·35 | 3·46–3·59 | 4·04–4·44 |
| (56) | 6·47–7·50 | 19·26–22·73 | 8·36–9·70 | 12·27–13·76 |

SCHEME 7

## EXPERIMENTAL

The low resolution mass spectra were recorded on an LKB 9000 instrument using the direct inlet system. The temperature of the inlet system was kept at 20 to 50 °C and that of the ion source at 270 °C. The electron energies used were 10 and 70 eV (nominal, noncalibrated values). Spectra of an epimeric pair were run under identical conditions, which includes the fact that the two epimers were processed consecutively, normally within an hour.

A computer system, connected on-line to the mass spectrometer, and comprising a 2310-C Raytheon Miniverter A/D converter, an HP (type 2116-B) 16-K computer, a plotter, a screen and a teletype was used. At the end of each scan the spectral data were read on to a magnetic disc. Using computer programs developed in this laboratory, the total ion intensity, $\Sigma_{40} I$, and the relative abundance expressed as a percentage of the intensity of the strongest peak, assigned the value 100, and of $\Sigma_{40} I$ were calculated. On average ten spectra of each compound were recorded at both the high and low electron voltage. The recorded spectra were checked by displaying them on the screen, and one spectrum of each compound was plotted out. Computer aided calculation of the intervals at 95 and 99% confidence levels was undertaken subsequently for the total ion currents and the intensities of selected peaks in these spectra.

Accurate mass measurements were performed on an Atlas SM-1 instrument using the direct inlet system; ion source temperature 250 °C, electron energy 70 eV. N.m.r. spectra were recorded on a Varian A-60 spectrometer and i.r. spectra on a Perkin–Elmer 257 instrument.

*Stachan-1α-ol* (1) *and stachan-1β-ol* (2). Stachan-1α-ol (1), m.p. 155 to 157 °C, Mol. wt.-m.s. 290 and stachan-1β-ol (2), m.p. 82 to 87 °C, Mol. wt.-m.s. 290, were readily prepared by catalytic hydrogenation (Pd/C, 10%, 2 h) of stach-15-en-1α-ol (3)[20] and stach-15-en-1β-ol[21] (4), respectively.

*2α-Hydroxymanoyl oxide* (7) *and 2β-hydroxymanoyl oxide* (8). A solution of 60 mg of 2-oxo manoyl in 20 ml of ether was stirred with 100 mg of lithium aluminium hydride at room temperature for 1 h. Work up in the usual manner and chromatography over silica gel (benzene–ether 1:0 → 3:1) afforded 50 mg of 2β-hydroxymanoyl oxide (8) m.p. 82 to 83 °C (reported 81 to 82 °C).[46]

To a solution of 60 mg of 2-oxo manoyl oxide in 10 ml of ethanol was added small pieces of sodium. After 0·5 h the reaction mixture was diluted with water and extracted with ether. Chromatography over silica gel gave 40 mg of 2α-hydroxymanoyl oxide (7) m.p. 56 to 59 °C (reported 57 to 59·5 °C).[46]

*2α-Hydroxy-1,1,2α,3,3-d$_5$-manoyl oxide* (7a) *and 2β-hydroxy-1,1,2α,3,3-d$_5$-manoyl oxide* (8a). To a solution of 20 mg of sodium in 2·5 ml of *O*-deutero-methanol and 0·5 ml of deuterium oxide was added 140 mg of 2-oxo manoyl oxide. The reaction mixture was refluxed under nitrogen for 2 h. The solvents were evaporated under reduced pressure. The residue was dissolved in 2 ml of *O*-deutero-methanol and 0·5 ml of deuterium oxide, and the mixture was again refluxed under nitrogen for 4 h. Half of the reaction mixture was removed, diluted with deuterium oxide and extracted with ether. The ether extract, containing 1,1,3,3-$d_4$-2-oxo-manoyl oxide, was dried and boiled under reflux with excess lithium aluminium deuteride for 1 h. Work up and chromatography over silica gel (benzene–ether 1:0 → 3:1) gave 30 mg of 2β-hydroxy-1,1.2α 3,3-$d_5$-manoyl oxide (8a) m.p. 82 to 83 °C Mol. wt.-m.s. 311; Isotopic composition: 20% $d_4$ 80% $d_5$.

The remainder of the reaction mixture containing the deuterated ketone was evaporated and diluted with 2 ml of *O*-deutero-ethanol. Small pieces of sodium were added over a period of 15 min.

The reaction mixture was then refluxed with sodium amalgam for 1 h. Dilution with water, extraction with ether and chromatography over silica gel (benzene–ether 1:0 → 3:1) gave 2α-hydroxy-1,1,2β, 3,3-$d_5$ manoyl oxide (7a), m.p. 60 to 61 °C, Mol. wt.-m.s. 311; Isotopic composition: 15% $d_4$, 81% $d_5$, 4% $d_6$.

*Methyl* 16-*norisopimar*-7-*en*-2α-*ol*-15-*oate* (9) *and methyl* 16-*norisopimar*-7-en-2β-*ol*-15-*oate* (10). To a solution of 100 mg of sodium borohydride in 5 ml of methanol was added 40 mg of methyl 16-norisopimar-7-en-2-on-15-oate.[22] The reaction mixture was kept at room temperature for 2 h. Dilution with water, extraction with ether and chromatography over silica gel furnished 25 mg of methyl 16-norisopimar-7-en-2β-ol-15-oate (10), which on recrystallisation from aqueous methanol and hexane followed by sublimation had m.p. 135 to 137 °C, Mol. wt.-m.s. 320.

Treatment of 30 mg of methyl 16-norisopimar-7-en-2-on-15-oate with a mixture of 1 ml of aqueous sodium hydroxide (50%) and 4 ml of ethanol at reflux temperature under nitrogen for 2 h gave 16-norisopimar-7-en-2-on-15-oic acid, which on recrystallisation from aqueous methanol had m.p. 208 to 211 °C (dec.). To a solution of 18 mg of this keto acid in 3 ml of ethanol was added small pieces of sodium over a period of 0·5 h at reflux temperature. The reaction mixture was diluted with water and extracted with ether. The product obtained was treated with ethereal diazomethane and chromatographed over silica gel to give 12 mg of methyl 16-norisopimar-7-en-2α-ol-15-oate (9), which on recrystallisation from hexane followed by sublimation had m.p. 112 to 113 °C, Mol. wt.-m.s. 320.

3β-$d_1$-16-*Norpimar*-7-*en*-3α-*ol* (11a) *and* 3α-$d_1$-16-*norpimar*-7-*en*-3β-*ol* (12a). A solution of 250 mg of 16-norpimar-7-en-3-one in 10 ml of dry ether was refluxed with 100 mg of lithium aluminium deuteride for 0·5 h. Work-up in the usual manner gave a mixture of two alcohols, which was separated on silica gel using a hexane–isopropyl ether gradient. The most nonpolar fraction consisted of 15 mg of 3β-$d_1$-16-norpimar-7-en-3α-ol (11a), which on recrystallisation from isopropyl ether had m.p. 110 to 111 °C, undepressed on admixture with the corresponding nondeuterated material;[22] Mol. wt.-m.s. 277; Isotopic composition: 94% $d_1$, 6% $d_2$.

The more polar fraction comprised 224 mg of 3α-$d_1$-16-norpimar-7-en-3β-ol (12a), which on recrystallization from isopropyl ether had m.p. 157 to 158 °C, undepressed on admixture with the corresponding nondeuterated material;[22] Mol. wt.-m.s. 277; Isotopic composition: 94% $d_1$, 6% $d_2$.

12-O-*Methylferruginol*-7α-*ol* (21) *and* 12-O-*methylferruginol*-7β-*ol* (22). A solution of 190 mg of sugiol methyl ether in 5 ml of ether was refluxed with excess lithium aluminium hydride for 0·5 h. Work-up in the usual manner and chromatography over silica gel furnished 7 mg of 12-*O*-methylferruginol-7α-ol (21), m.p. 75 to 80 °C, n.m.r. peak at 4·77 ppm (m, $W_{1/2} \sim 6$) Mol. wt.-m.s. 316 and 93 mg of 12-*O*-methylferruginol-7β-ol (22) as a gum; n.m.r. peak at 4·80 ppm (broadened t, $J(AX) + J(BX) \sim 16$), Mol. wt.-m.s. 316.

*Totarol*-7α-*ol* (23) *and totarol*-7β-*ol* (24). To a solution of 200 mg of totarol-7-one in 2 ml of dry dioxane was added 100 mg of lithium aluminium hydride in 10 ml of ether. The reaction mixture was refluxed for 0·5 h. Dilution with ice water and aqueous sulphuric acid, extraction with ether followed by chromatography over silica gel afforded 39 mg of totarol-7α-ol (23), which on recrystallisation from benzene had m.p. 210 to 211 °C, Mol. wt.-m.s. 302 and 66 mg of totarol-7β-ol (24), m.p. 199 to 200 °C (reported m.p. 200 to 201 °C).[47]

*Methyl* 12α-*hydroxypodocarpan*-18-*oate* (29) *and methyl* 12β-*hydroxy-podocarpan*-18-*oate* (30). A solution of 52 mg of methyl 12-oxo-podocarpan-18-oate[48] in 7 ml of methanol was stirred with 50 mg of sodium borohydride at 0 °C for 1 h. The reaction mixture was acidified, diluted with water and extracted with ether. The mixture of alcohols obtained was separated on silica gel (hexane–acetone 19:1) to give 4 mg of methyl 12α-hydroxypodocarpan-18-oate (29) as a gum; n.m.r. peak at 4·18 ppm $W_{1/2} \sim 6$, Mol. wt.-m.s. 294 and 24 mg of methyl 12β-hydroxypodocarpan-18-oate (30) as a gum; n.m.r. peak at ~ 3·6 ppm (broad m), Mol. wt.-m.s. 294.

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