**1195.** *Mass Spectra and Organic Analysis. Part VI.[1] The Mass Spectra of Menthone, Isomenthone, and Carvomenthone*

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The mass spectra of menthone, isomenthone, and carvomenthone have been examined. Menthone was labelled on every carbon atom with deuterium, thus enabling a detailed study of the fragmentation pattern to be made. The simpler pattern of carvomenthone is also discussed.

CONTINUING our work on monoterpenoids,[2] we wished to make a detailed study of the saturated cyclic ketones and in particular to ascertain how these differed from simpler cyclohexanones,[3,4] and in this Paper we report our results on the saturated menthane ketones.
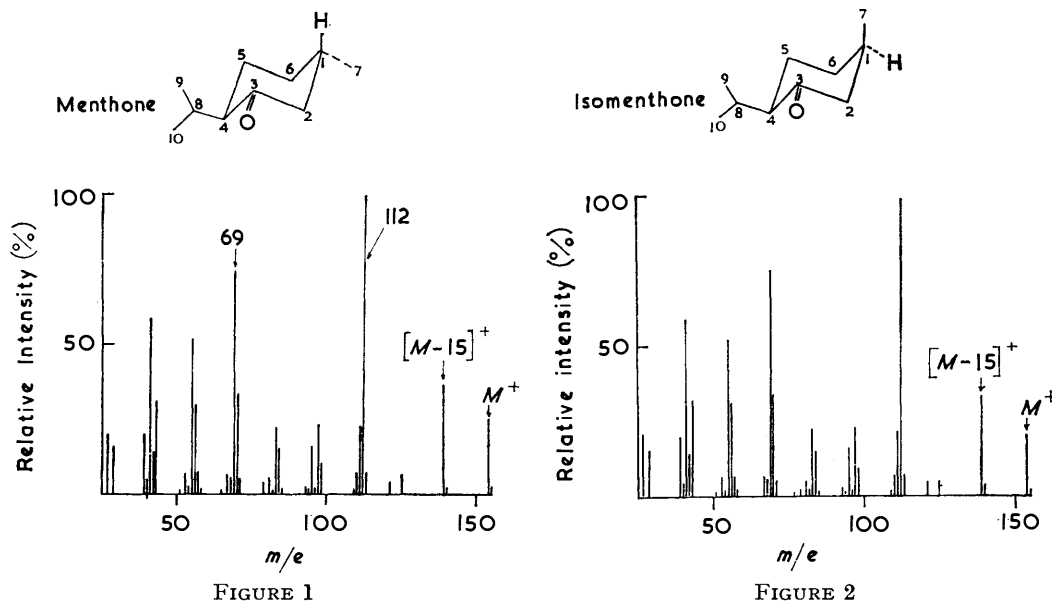
FIGURE 1

FIGURE 2

The mass spectra of menthone (Figure 1) and isomenthone (Figure 2) have been previously reported,[5-7] and it is first necessary to clear up one anomaly. Although Budzikiewicz, Djerassi, and Williams stated [6] that the main fragment at m/e 112 in menthone did not arise from loss of $COCH_2$ from the ring since it shifted to m/e 115 in the 2,2,4-trideuterated compound (Figure 4) (contrary to Reed's earlier suggestion [5]), von Sydow again writes a dotted line on his menthone formula [7] implying that this is a possible fragmentation. We have shown by further deuteration experiments (below) that Budzikiewicz's suggestion is unquestionably correct, but the earlier idea would in any case have been surprising in view of the observation that in carvomenthone (Figure 3) the only fragment in this region is at

[1] Part V, A. F. Thomas and B. Willhalm, *Tetrahedron Letters*, 1964, 3177.
[2] Part IV, B. Willhalm, A. F. Thomas, and M. Stoll, *Acta Chem. Scand.*, 1964, **18**, 1573.
[3] J. Seibl and T. Gäumann, *Z. analyt. Chem.*, 1963, **197**, 33; *Helv. Chim. Acta*, 1963, **46**, 2857.
[4] D. H. Williams, H. Budzikiewicz, Z. Pelah, and C. Djerassi, *Monatsh.*, 1964, **95**, 166.
[5] R. I. Reed, " Mass Spectrometry of Organic Ions," ed. F. W. McLafferty, Interscience, New York, 1963, ch. 13.
[6] H. Budzikiewicz, C. Djerassi, and D. H. Williams, " Interpretation of Mass Spectra of Organic Compounds," Holden-Day, San Francisco, 1964. We do not dispute the statement that traces of isomenthone do not affect deductions about the mass spectrum of menthone.
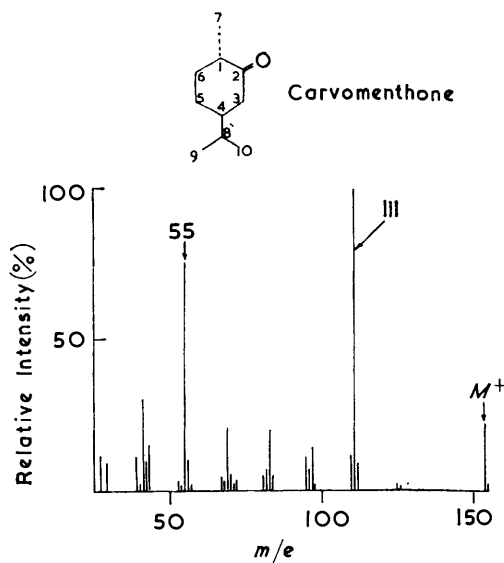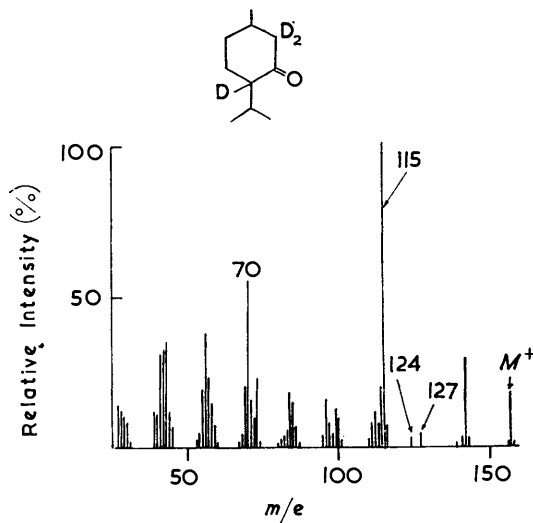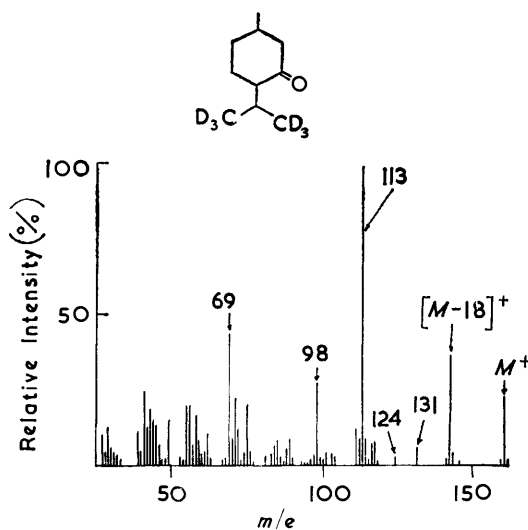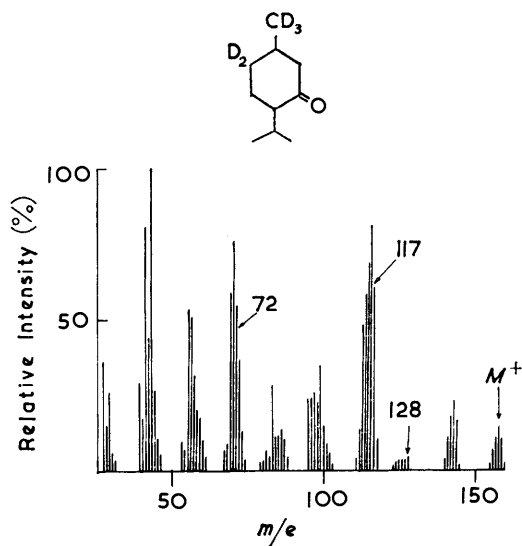[7] E. von Sydow, *Acta Chem. Scand.*, 1964, **18**, 1099.

FIGURE 3

FIGURE 4

FIGURE 5

FIGURE 6

m/e 111 ($M - 43$) corresponding to loss of the isopropyl side-chain, a fission of great ease in many menthane derivatives.[8,9]

Despite the report [6] that the mass spectra of menthone and isomenthone are " virtually identical," there is, in fact, a significant difference. The molecular ion is measurably more stable in menthone than in isomenthone (respectively 3·56 and 2·82% of the total ionisation Σ 27), an observation originally made by Natalis [10] on the *trans-* and *cis*-isomers of methylcyclohexanes, and which we have observed on *trans-* and *cis*-menthanes.[8]

[8] A. F. Thomas and B. Willhalm, *Helv. Chim. Acta*, 1964, **47**, 475.

[9] H. Budzikiewicz, C. Djerassi, and D. H. Williams, " Structure Elucidation of Natural Products by Mass Spectrometry," vol. II, Holden-Day, San Francisco, 1964.

[10] P. Natalis, *Bull. Soc. chim. belge*, 1960, **69**, 519; 1964, **73**, 961.

Furthermore, the fragment at $(M - 15)^+$ is also more stable in menthone than in iso-menthone, and we felt that this might correspond to loss of methyl from the isopropyl side-chain, rather than from C-1 which would have removed any strain difference between the two. This was indeed the case, as shown by the mass spectrum of menthone terminally deuterated in the isopropyl group (Figure 5) and in the methyl group attached to C-1 (Figure 6). We have previously mentioned that methyl groups are not easily lost when other fragmentations are available, and here too, the *number* of methyl groups is not the reason for the important $(M - 15)^+$ fragment (as has been suggested [11]), but rather the favourable nature of the transition shown in Scheme 1.* It is therefore not surprising that the $(M - 15)^+$ fragment in carvomenthone is barely perceptible.
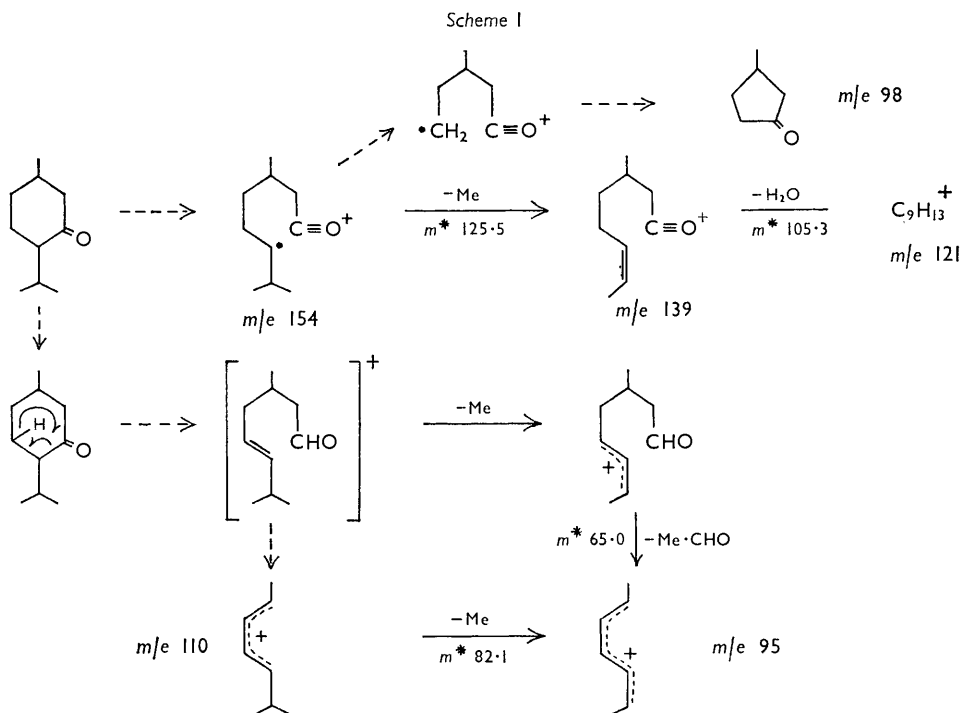
Scheme I

The formation of the fragment at m/e 98 from menthone can be followed in the deuterated compounds since it is the heaviest of the group, and appears to involve the loss of C-4 and the side-chain, as shown in Scheme 1. The corresponding fragment from carvomenthone (formed by loss of C-1 and its methyl group) visible at m/e 126 is much less important.

It is likely that most of the fragment at m/e 95 from menthone arises from the fragment of mass 139 (weak metastable peak at about m/e 65) or from the minor fragment at m/e 110 (shifted to m/e 116 in Figure 5, metastable peak at m/e 82·1). In the hexadeuterated compound (Figure 5), it would appear from the height of the peak that both the m/e 95 and 97 fragments have been shifted to m/e 98 (which furthermore contains the m/e 98 fragment unchanged). Figure 8 shows that some of the hydrogen at C-5 is lost in the formation of both the 110 and 95 fragments. Nevertheless, there are fragments with insufficient

* In the " Schemes " we use the convention of Barnes and Occolowicz [12] that solid arrows represent transitions supported by the metastable peaks given alongside the arrows; dotted arrows represent supposed transitions for which no metastable peak was observed.

[11] B. Willhalm, A. F. Thomas, M. Stoll, and E. G. E. Hawkins, *Helv. Chim. Acta*, 1963, **46**, 2098.
[12] C. S. Barnes and J. L. Occolowitz, *Austral. J. Chem.*, 1963, **16**, 219.

deuterium in Figure 6, and small fragments with more than that required in Figure 4, showing that minor pathways are available. A similar sequence will account for the formation of these fragments from carvomenthone.
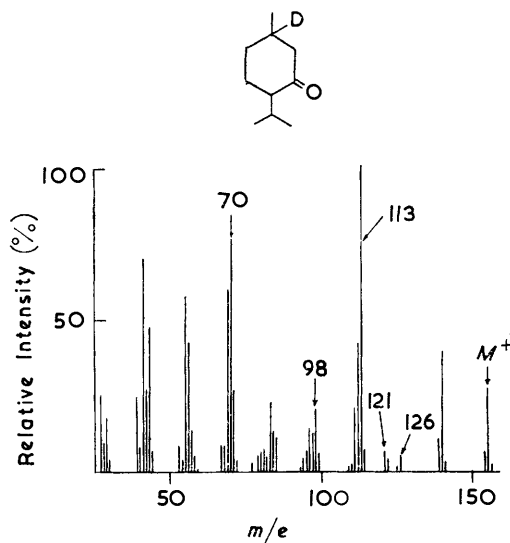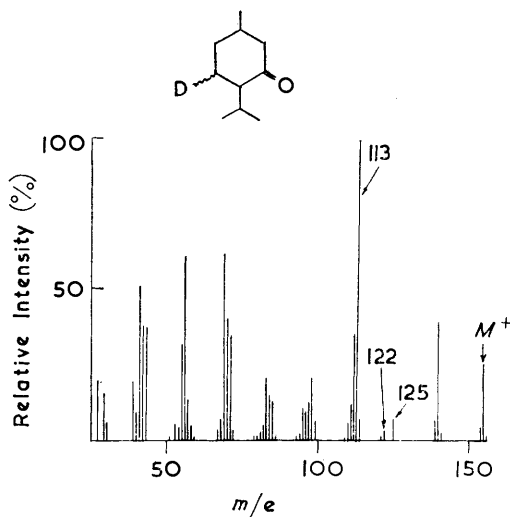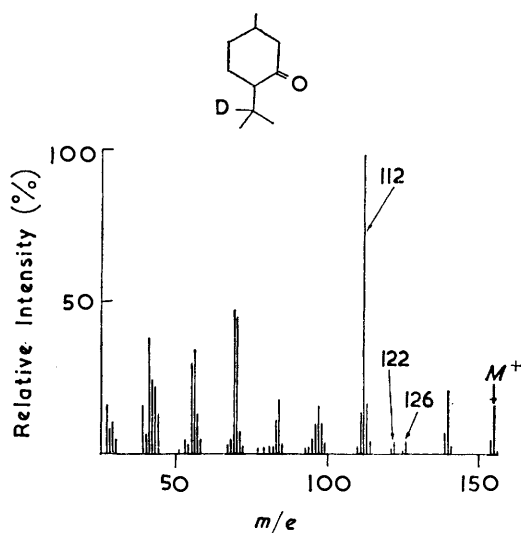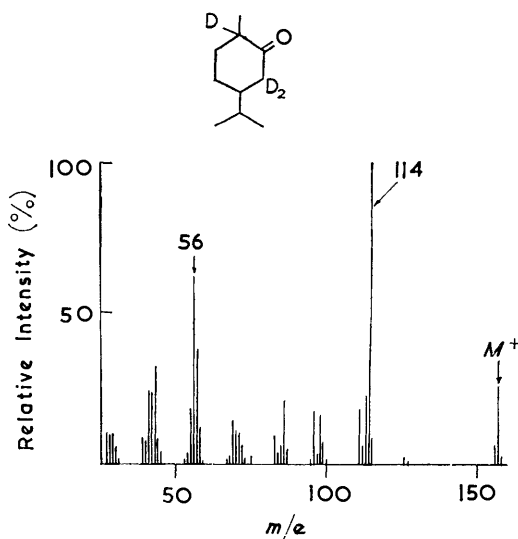

FIGURE 7

FIGURE 8

FIGURE 9

FIGURE 10

The fragment at m/e 121 arises from menthone by loss of H_2O from the fragment at m/e 139. The hydrogen atoms involved are not adjacent to the carbonyl group, so participation of an enol is excluded (cf. loss of water from cyclohexanone [4]). The mass spectrum of 1-deuteromenthone (Figure 7) shows that one of the hydrogens involved comes mostly from C-1, the remainder being supplied from C-5 (Figure 8) with possibly some from C-8 (Figure 9).

Menthone shows a fragment corresponding to loss of C_2H_5 at m/e 125. The side-chain is not involved (Figure 5), and the heaviest fragment of the group is at m/e 128

in Figure 6, so the two carbon atoms involved are C-5 and C-6 (confirmed by Figure 8). One hydrogen atom is transferred (presumably from C-2, see Figure 4), and the sequence must be the relatively simple one shown in Scheme 2—in contrast to the complex rearrangement needed to explain the loss of C_2H_5 from cyclohexanone.[4]
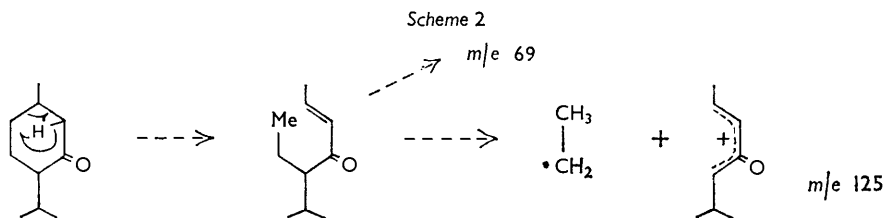
Scheme 2

The main fragmentation to m/e 112 occurs, as stated above, by the cyclic process involving transfer of one hydrogen atom from the side-chain to the carbonyl (Scheme 3).

Scheme 3
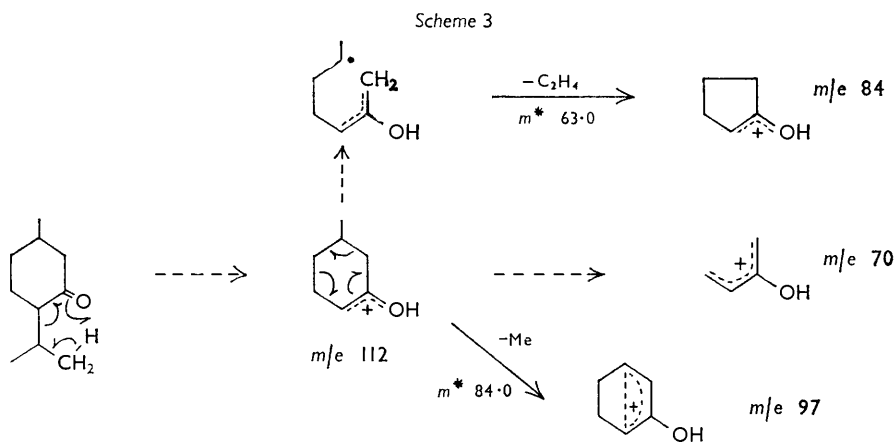
Fission of $COCH_2$ from flexible alicyclic ketones is a very unfavourable process; it does not occur in carvomenthone (Figure 3) where the principal fragment at m/e 111 arises by simple fission of the isopropyl group, shifting to m/e 114 in the 1,3,3-trideuterated compound (Figure 10). (Menthone also shows simple isopropyl fission to a minor extent.) The only monoterpene ketone we have so far proved to lose keten is camphor,[13] but this is a rigid system, as are the steroid ketones and decalones* that have also been shown to lose 42 mass units,[9,14] The fragment of mass 112 is probably the enolic form of 3-methylcyclohexanone, which explains the fact that it undergoes subsequent fission in a somewhat different way from the ketone.[3] Apart from loss of methyl to m/e 97, an important mode of fragmentation is *via* a retro-Diels–Alder reaction to a fragment at m/e 70. The fragment is displaced to m/e 73 in Figure 4 and to m/e 71 in Figure 5, remaining at m/e 70 in Figure 8. There appears to be another less important route to the fragment at m/e 70, judging by the intensity of the m/e 71 fragment in Figure 7 (see below and Scheme 5).

The fragment at m/e 84 has been reported[7] to arise from the fragment at m/e 112, and indeed there is a strong metastable peak at m/e 63·0. There is hardly any fragment in Figure 4 at m/e 87 corresponding to simple loss of CO, and in Figure 6, the fragments at

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* *trans*-8-Methylhydrindan-2-one also has recently been shown to lose keten.[13a]

[13] A. F. Thomas and B. Willhalm, unpublished observation, confirmed by deuteration studies. The mass spectrum of camphor has been published by von Sydow (ref. 7).

[13a] J. Karliner, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1965, **87**, 580.

[14] *E.g.*, R. H. Shapiro and C. Djerassi, *J. Amer. Chem. Soc.*, 1964, **86**, 2825.

m/e 86 and 87 indicate that two or three deuteriums remain in the ion at this stage. Judging from the hexadeuterated menthone (Figure 5), this fragment is not very specific, but we would suggest that one of the main pathways is by formation of the enol of cyclo-pentanone (Scheme 3).

The fragment at m/e 83 appears to involve the side-chain (Figure 5) and remains at 83 in Figure 6. The most reasonable explanation involves hydrogen transfer from one of the side-chain carbons (unspecific), as shown in Scheme 4.

Scheme 4
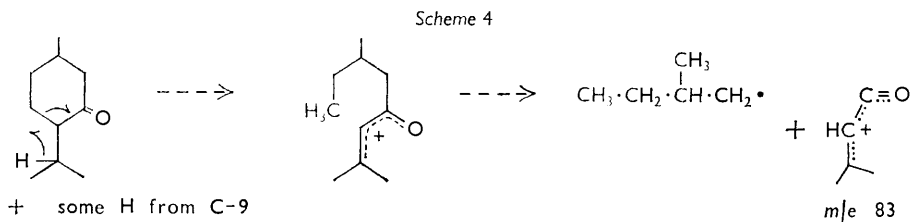
There must exist several different routes leading to the remaining fragments, though, as may be seen from Figure 5, there is little evidence of randomisation of hydrogens—at least between the side-chain and ring. For example, that part of the isopropyl ion at m/e 43 contributed by the side-chain is cleanly moved to m/e 49, just as the $C_4H_7{}^+$ ion can be seen to contain none, three, or six deuteriums. One fragmentation leading to the ion at m/e 55 involves fission of the C-1-C-2 and C-4-C-5 bonds to leave carbon atoms 1, 5 and 6 and the methyl group. In menthone this is not the main route to the ion, but in carvomenthone, the weakness of the C-1-C-2 bond makes this a highly favoured fission, and the important fragment at m/e 55 is mostly shifted to m/e 56 in 1,3,3-trideuterated carvomenthone (Figure 10, Scheme 6). The fragment at m/e 69 is somewhat more specific in that it includes carbon atoms 1, 2, and 3 and the methyl group, though it is more doubtful from which ion it is formed. There is a metastable peak at m/e 43 (111 ⟶ 69), but there are clearly several possibilities of the type shown in Scheme 5.
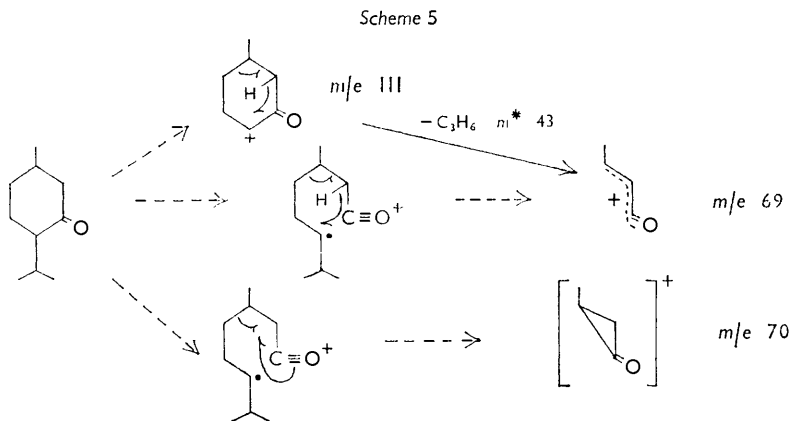
Scheme 5

The mass spectrum of carvomenthone is simpler than that of menthone, two of the main fragmentations (loss of ethyl and side-chain fission with H-transfer) being unfavourable. A similar fission (to m/e 110 and 95) to that shown in Scheme 1 occurs (supported again by the metastable peak at m/e 82·1). The base peak at m/e 111 appears to split in two directions, on one or the other side of the carbonyl group, leading to the C_4 fragment at m/e 55 directly or through a C_6 fragment, as shown in Scheme 6.

Scheme 6

C ≡ O$^+$ m/e 154 m/e 55

m* 27.3   m* 36.4

C ≡ O$^+$ m* 62.2   m/e 83

m/e 111
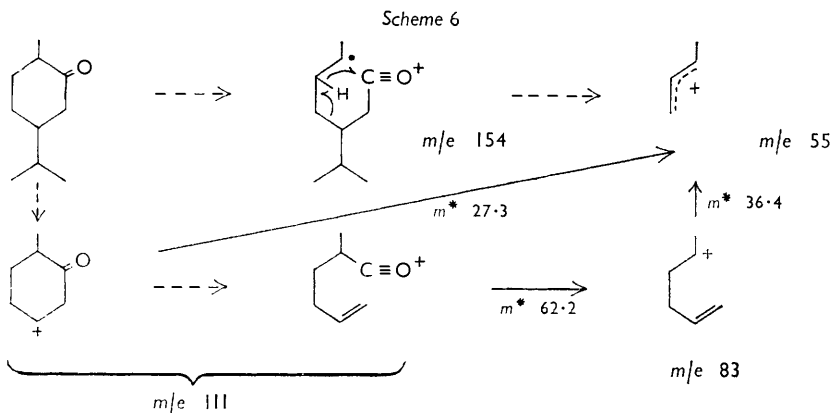
EXPERIMENTAL

Mass spectra were measured on an Atlas CH-4 apparatus with bombarding electrons of 70ev energy. Temperature of source 275°, temperature of introduction 150°. Gas chromatography was carried out on a Carbowax (15%) on Chromosorb W column at 200° mounted in a type 59T gas chromatography apparatus of the Société d'électronique et de mécanique d'Aquitaine, Pau, France (manufactured under licence from Firmenich & Cie).

Materials.—Menthone and isomenthone were obtained by gas-chromatographic separation from a distilled sample of commercial menthone. Carvomenthone was obtained by catalytic reduction (palladium–charcoal) of commercial carvone.[15] In view of the difficulty of separating the isomers by gas-chromatography, mass-spectroscopic measurement was carried out on the mixture. 2,2,4-[^{2}H$_3$]Menthone and 1,3,3-[^{2}H$_3$]carvomenthone were prepared by deuterium exchange in dioxan–D$_2$O with a trace of NaOD (isotopic purity: [^{2}H$_3$]menthone, 91%; [^{2}H$_2$]-menthone, 9%; [^{2}H$_3$]carvomenthone, 82%; [^{2}H$_2$]carvomenthone, 16%).

1-[^{2}H]*Menthone.*[16] Redistilled piperitone (50 mg.) was added to a solution of lithium (25 mg.) in liquid [^{2}H$_3$]ammonia (*ca.* 7 c.c.) prepared from magnesium nitride (20 g.) in ground-nut oil (50 ml.) and deuterium oxide (20 g.). Improved yields of [^{2}H$_3$]ammonia were obtained by using an ice–salt condenser at −15° at the exit of the vessel containing the nitride in oil, and, using a slow current of dry nitrogen, passing the gases through a tube of magnesium nitride and calcium oxide before condensing the ammonia in the reaction vessel. In later experiments when the reaction was finished, most of the deuterated ammonia was distilled into a second vessel and used again. The excess of lithium was decomposed with methanol, water was added, and the mixture heated 30 min. under reflux. The deuterated product was isolated with pentane and purified by gas chromatography (isotopic purity 82%).

5-[^{2}H]Menthone was prepared in a similar manner from menth-3-ene-5-one[17] (isotopic purity 85%). 8-[^{2}H]Menthone was prepared in a similar manner from pulegone (isotopic purity 75%).

1,3-[^{2}H$_6$]*Isopropyl iodide.* [^{2}H$_6$]Acetone (5 g. in dry ether, 20 ml.) was added slowly to a slurry of lithium aluminium hydride (1·5 g.) in dry ether (10 ml.). Water (2·8 ml.) was added, and the ether removed almost completely. To the residue was added hydriodic acid (48%; 50 ml.) and the mixture slowly distilled. The upper layer of the distillate was returned to the distillation flask until no more product distilled. Recovery of the iodides from pentane gave 8·5 g. 1,3-[^{2}H$_6$]isopropyl iodide containing a trace of ethyl iodide.

9,10-[^{2}H$_6$]Piperitone[18] was made from ethyl sodioacetoacetate and 1,3-[^{2}H$_6$]isopropyl iodide followed by reaction with freshly distilled but-3-en-2-one. The yield of [^{2}H$_6$]piperitone after distillation was 1·4 g. (11·5% based on the [^{2}H$_6$]acetone used).

[15] Leading references to these reductions may be found in, *e.g.*, " Die Aetherischen Oele," E. Gilde-meister and F. Hoffmann, vol. IIIc, 4th edn., Akademie-Verlag, Berlin, 1963.
[16] Cf. D. H. Williams, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1963, **85**, 2091.
[17] G. Ohloff and G. Uhde, *Helv. Chim. Acta*, 1965, **48**, 10. We are grateful to these authors for a sample of menth-3-ene-5-one.
[18] Cf. S.-O. Lawesson, E. H. Larsen, and H. J. Jakobsen, *Rec. Trav. chim.*, 1964, **83**, 464.

9,10-[^{2}H$_6$]Menthone [15] was obtained by catalytic reduction in ethanol (palladium–charcoal) of the piperitone previously described, and purified by gas-chromatography (isotopic purity: 9,10-[^{2}H$_6$]menthone, 96·1%; 9,10-[^{2}H$_5$]menthone, 4%).

6,7-[^{2}H$_5$]*Menthone*. Piperitone was exchanged in dioxan–deuterium oxide as described above. The isotopic purity after two such exchanges obtained was [^{2}H$_7$]- 43%, [^{2}H$_6$]- 39%, [^{2}H$_5$]-piperitone 14%. Catalytic reduction in alcohol in presence of palladium–charcoal was complete in 15 min., and the mixture was diluted immediately with water, and the menthone isolated with pentane. Back-exchange of the product with water–dioxan and a trace of sodium hydroxide gave 6,7-[^{2}H$_5$]menthone (isotopic purity: [^{2}H$_5$]- 23%; [^{2}H$_4$]- 31%; [^{2}H$_3$]- 26%; [^{2}H$_2$]-menthone, 15%).

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