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Mass Spectrometry of Substituted 1,3-Dihydro-2*H*-imidazole-2-thiones

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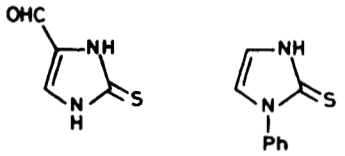
The electron impact mass spectra of the 4-formyl-1, 3-dihydro-2*H*-imidazole-2-thione, its six 1-methyl(*n*-propyl, *n*-hexyl)-3-methyl(phenyl)-disubstituted derivatives, and the 1,3-dihydro-1-phenyl-2*H*-imidazole-2-thione are discussed. The fragmentation pattern is strongly influenced by the alkyl or phenyl *N*-substituents, as well as by the length of the alkyl chain. The odd-electron ions containing an *N*-phenyl substituent, but not a propyl or hexyl group, eject a hydrogen atom from the phenyl ring, while the presence of a long alkyl chain greatly enhances the loss of the sulphyhydryl radical and facilitates the expulsion of several alkenes, and alkyl and alkenyl radicals.

INTRODUCTION

1,3-Dihydro-2*H*-imidazole-2-thione derivatives are important because of the pharmacological properties associated with some compounds of this type. Nevertheless, mass spectrometric data on these compounds are very scarce, as only the spectra of the simple heterocycle and its 1-methyl derivative have been reported.[1] In order to study the mass spectrometric behaviour of the formyl, alkyl and phenyl derivatives, the 4-formyl and 1-phenyl derivatives **1** and **2**, the 1-alkyl-3-methyl-substituted aldehydes **3** and the 1-alkyl-3-phenyl-substituted aldehydes **4** were examined. The comparison of the results with the mass spectra of compounds having related structures permits a better understanding of the fragmentation pattern of these heterocyclic derivatives.



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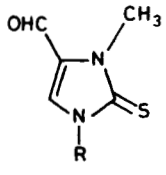

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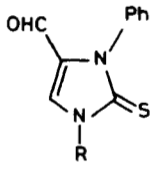

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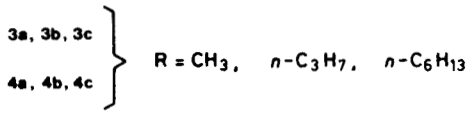

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In compounds **1** and **2**, there is a thione/thiol equilibrium, probably shifted towards the thione tautomer, as observed in related compounds.[2] The spectra were obtained using electron impact ionization (70 eV) and the composition of all ions discussed was confirmed by accurate mass measurements. Deuteration experiments and metastable transitions in the second field-free region were utilized to support the fragmentation pathways.

RESULTS AND DISCUSSION

The fragmentation pathway proposed from the mass spectrum of aldehyde **1** (Fig. 1) is depicted in Scheme 1. As in the imidazole-4(5)-carboxaldehyde,[3] the molecular ion gives rise to the base peak, and the consecutive losses of H$^{\cdot}$ and CO, along with the direct ejection of CO, constitute the primary fragmentations. In the *N,N*-dideuterated analogue, the *m/z* 99 peak is shifted 2u indicating that the hydrogen atom is expelled from the formyl group. The proposed mechanism for the loss of $NH_2^{\cdot}$ from the *m/z* 99 is supported by the loss of $ND_2^{\cdot}$ observed in the deuteration experiment. The $[M-CO]^{+\cdot}$ ion decomposes in the same way as the molecular ion does in the simple heterocycle.[1] With respect to the interpretation of the spectrum of this last compound reported earlier,[1] it must be pointed out that an obvious slip was made, since the ion at *m/z* 41 cannot derive from the *m/z* 73 by loss of SH$^{\cdot}$. Our findings in **1** indicate that the *m/z* 41 ion derives from the $[M-CO]^{+\cdot}$ ion by elimination of HNCS. The peak at *m/z* 45 is due to the $[CHS]^+$ ion.

The mass spectrum of the phenyl derivative **2** shows a reduced number of significant peaks which correspond to the ions $M^{+\cdot}$ (95%), $[M-H]^+$ (100%), $[C_6H_5]^+$ (30%) and $[C_4H_3]^+$ (28%). The high abundance of the $[M-H]^+$ ion contrasts strikingly with the very low one shown for this ion in the 1,3-dihydro-2*H*-imidazole-2-thione and in its 1-methyl derivative.[1] In the *N*-deuterated analogue of **2**, the $[M-H]^+$ ion retains the deuterium

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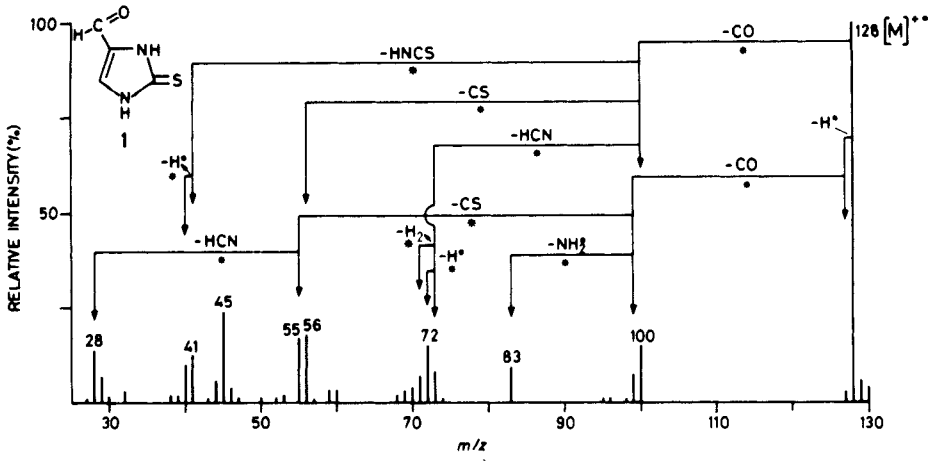
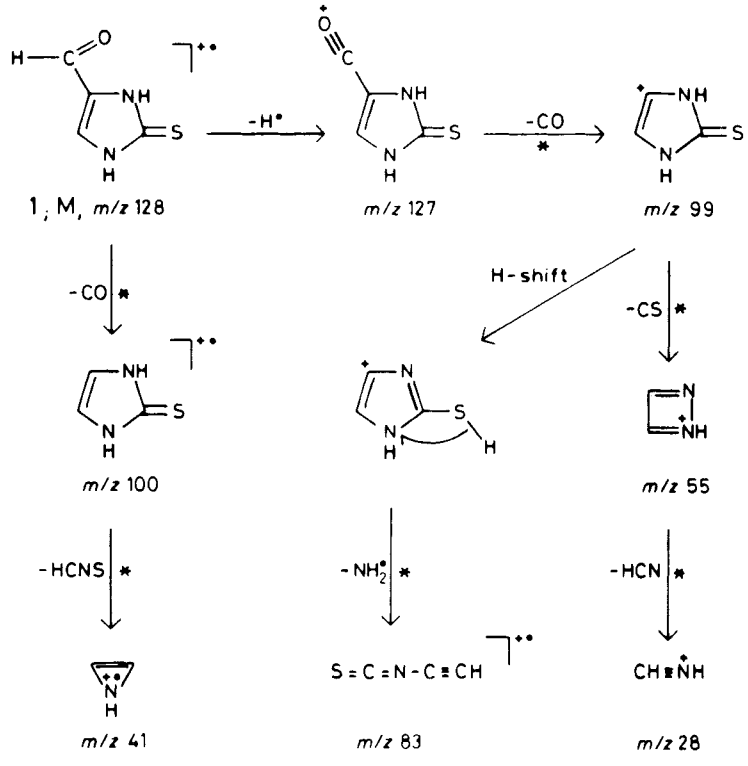


Figure 1. Mass spectrum (70 eV) of 4-formyl-1,3-dihydro-2*H*-imidazole-2-thione (**1**).

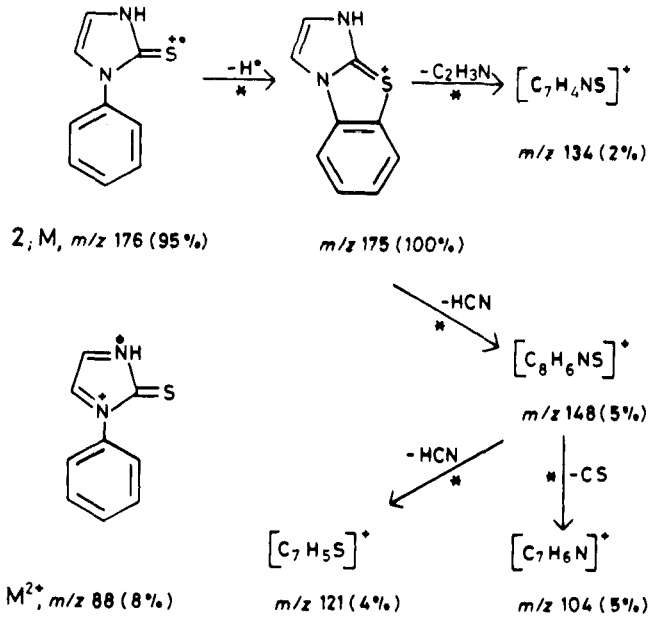
atom. These facts suggest that the hydrogen atom is expelled from the phenyl ring, yielding an ion at m/z 175 (Scheme 2) with a structure similar to that proposed for the $[M-H]^+$ ion in the phenyl thioureas.[4] The fragmentation routes from the $[M-H]^+$ ion are consistent with a structure possessing a sulphur atom attached to the phenyl ring. The formation of a double-charged molecular ion, also occurring in the simple heterocycle, is due to the possibility of separation of charges in a conjugated system.[5]

All spectra of 1,3-disubstituted aldehydes **3** and **4** exhibit an intense molecular peak, but depending on whether the nature of the substituents is alkylic or phenylic and also on the alkyl-chain, striking differences are observed in the abundances of the $[M-H]^+$ and $[M-SH]^+$ ions and in the fragmentation pathways. The molecular ions of both 4-formyl-1-methyl derivatives **3a** and **4a** (Fig. 2) directly decompose to the m/z 42 ion, probably via the mechanism (Scheme 3) proposed for a similar fragmentation in the 4-formyl- and 4-nitro-1-methylimidazoles,[3,6]. Nevertheless, in the 3-methyl derivative **3a**, the primary fragmentation renders the $[M-CO]^{+\cdot}$ ion, but in the 3-phenyl derivative **4a**, the loss of $H^\cdot$ from the molecular ion is the most important fragmentation process. This behaviour of **4a**, similar to that observed in **2**, and the common fragmentations from the m/z 148 ion in both compounds suggest that the hydrogen atom is lost from the phenyl ring (Scheme 3).

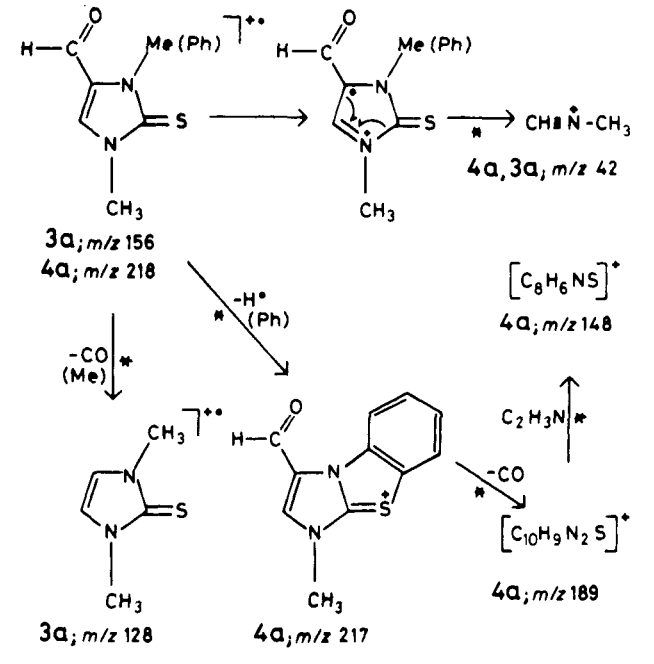
In **3a**, the $[M-CO]^{+\cdot}$ ion decomposes as indicated in Scheme 4. The m/z 127 ion is formulated in the same



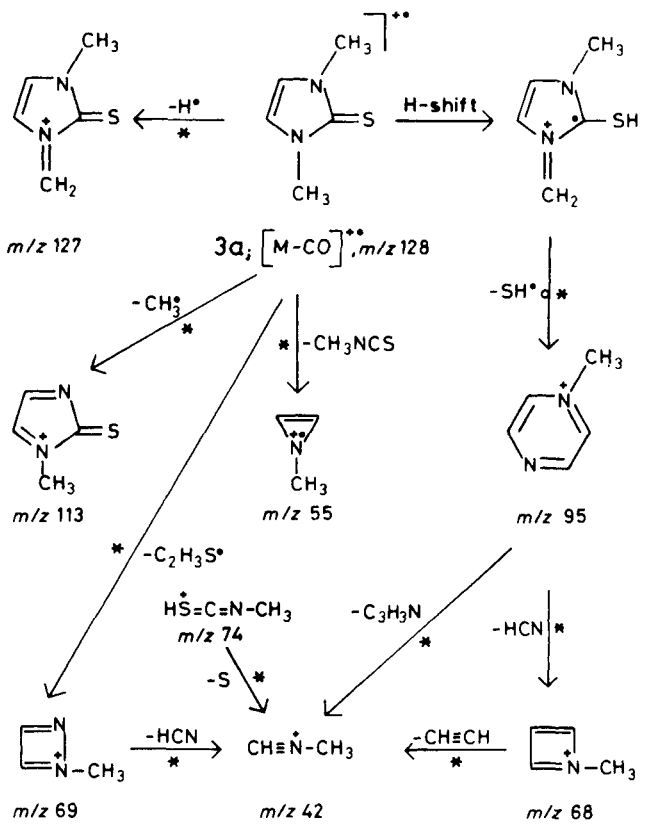
Scheme 1. Fragmentation of 4-formyl-1,3-dihydro-2*H*-imidazole-2-thione (**1**).



Scheme 2. Fragmentation of 1,3-dihydro-1-phenyl-2*H*-imidazole-2-thione (**2**).



Scheme 3. Principal fragmentations of 4-formyl-1,3-dihydro-1-methyl-3-methyl(phenyl)-2*H*-imidazole-2-thiones (**3a** and **4a**).



Scheme 4. Fragmentation from the $[M-CO]^{+\cdot}$ ion in 4-formyl-1,3-dihydro-1,3-dimethyl-2*H*-imidazole-2-thione (**3a**).

way as the $[M-H]^+$ ion in the 1-methylimidazole, where the hydrogen atom is expelled from the methyl group to a high degree of specifity.[7] The loss of SH$^\cdot$ from the $[M-CO]^{+\cdot}$ ion probably involves an H shift from the methyl group to the sulphur atom followed by a ring expansion, rendering the *m/z* 95 ion, whose structure is in agreement with the subsequent fragmentations. The *m/z* 42 ion is formed from several precursors in addition to that deriving directly from the molecular ion.

In the spectrum of **4a** (Fig. 2), it is worth commenting on the *m/z* 109 peak constituted by the double-charged molecular ion along with the $[C_6H_5S]^+$ ion which is also found in the spectra of phenyl thioureas.[8] The origin of the moderately abundant $[C_7H_7]^+$ ion at *m/z* 91 is unclear although its absence in **2** may have something to do with the presence of the methyl group.

Although the **3b**, **3c**, **4b** and **4c** compounds show an intense parent peak, the existence of the alkyl chain suppresses the loss of CO from the $M^{+\cdot}$ or $[M-H]^+$ ions, greatly reduces the abundance of the $[M-H]^+$ ion in the phenyl derivatives **4b** and **4c**, enhances the ejection of SH$^\cdot$ and originates several ions derived from the alkyl-chain cleavage. The spectra of **3c** and **4c**, which are considered as models of long-chain-substituted derivatives, are depicted in Fig. 3. The elimination of alkene involving the entire chain renders an abundant ion and can be envisaged as occurring by way of a McLafferty rearrangement, similar to that proposed for the thioureas,[8] followed by tautomerization to the stabler thione form (Scheme 5). In the 3-methyl derivatives **3b** and **3c**, the resultant ion at *m/z* 142 expels CO, rendering the *m/z* 114 ion which fragments in the same way as the 1,3-dihydro-1-methyl-2*H*-imidazole-2-thione.[1] In contrast, in the phenyl derivatives **4b** and **4c**, the *m/z* 204 ion ejects H$^\cdot$ from the phenyl ring, since the subsequent fragment ion at *m/z* 175 decomposes in the same way as the $[M-H]^+$ ion in **2**. The elimination of the alkenes involving a C(1)′–C(2)′ cleavage seems to proceed via an H shift from the alkyl chain to the C(1)′ atom, as happens in *N*-alkyl derivatives of succinimide and pyrrolidone,[9] because the resultant ions, *m/z* 156 and 218, fragment in the same way as the molecular ions in the 1-methyl derivatives **3a** and **4a**, respectively. The

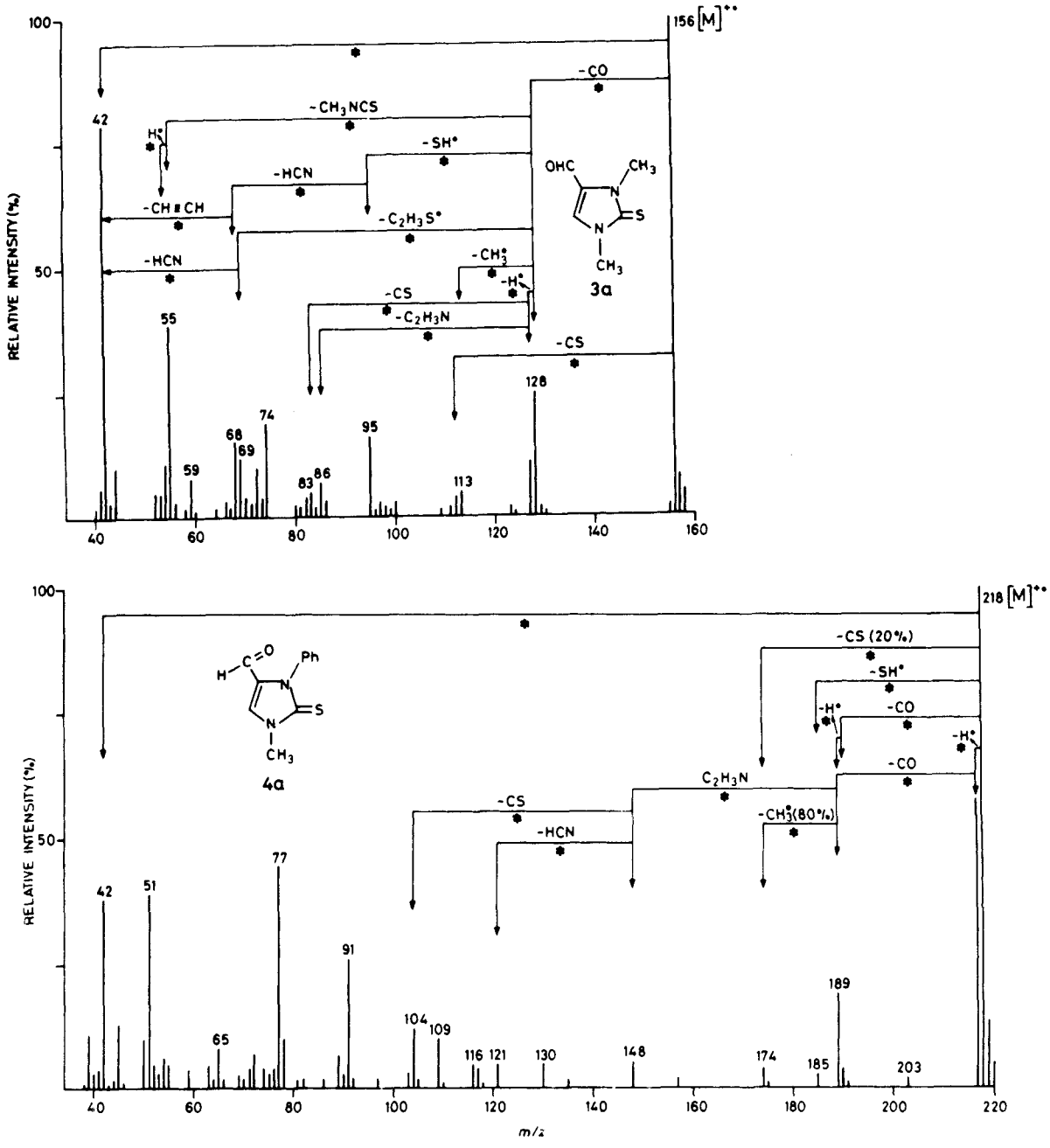


Figure 2. Mass spectra (70 eV) of 4-formyl-1,3-dihydro-1-methyl-3-methyl(phenyl)-2*H*-imidazole-2-thiones (**3a** and **4a**).

expulsion of the alkyl chain with double hydrogen rearrangement seems to occur in practically the same way as in *N*-alkyl-succinimides.[9] The hexyl derivatives **3c** and **4c** show an additional loss of C_4H_8 and a subsequent elimination of CO in the former and of H· in the latter. In sum, the ions resulting from alkene elimination lose CO when possessing a 3-methyl substituent, while ejecting H· in the case of a phenyl substitution.

In order to compare the abundances of the peaks due to the simple scissions of C′ – C′ bonds in the alkyl chain, only the **3b** and **3c** compounds have been considered because in the phenyl derivatives **4b** and **4c** there are interferences from isobaric ions arising from the [M – alkene]$^{+\cdot}$ ions by loss of H·. All the C′ – C′ bonds, except C(1)′ – C(2)′, are broken, although the major peak originates from the C(2)′ – C(3)′ bond cleavage. This behaviour might be explained by the formation of cyclic structures (Scheme 6) like those proposed for similar ions in the *N*-alkyl-pyrrolidones.[10] The alkyl chain also gives rise to the appearance of hydrocarbon fragment ions, principally the species $[C_3H_5]^+$, at *m/z* 41.

Regarding the loss of SH· from the molecular ion, three facts are taken into account: the abundance of the $[M-SH]^+$ ion is negligible in **3a** and **4a** (2 and 3%, respectively) and becomes increasingly important in the higher homologues (15% in the propyl derivatives **3b** and **4b**, and 100% in the hexyl derivatives **3c** and **4c**); there is no relation between the abundances of the $[M-SH]^+$ ion and the alkylic or phenylic nature of the 3-substituent; finally, no evidence of any further frag-

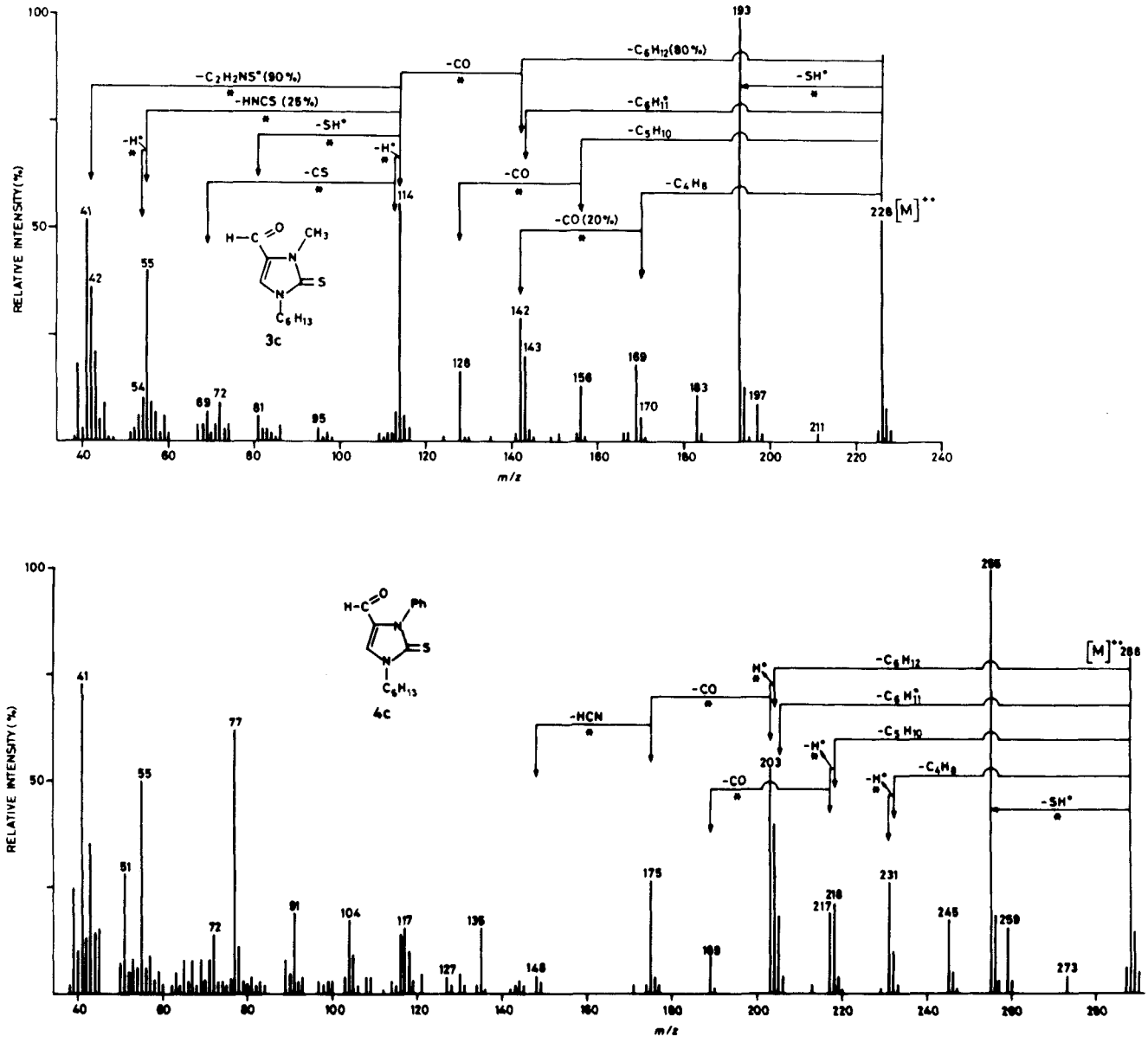


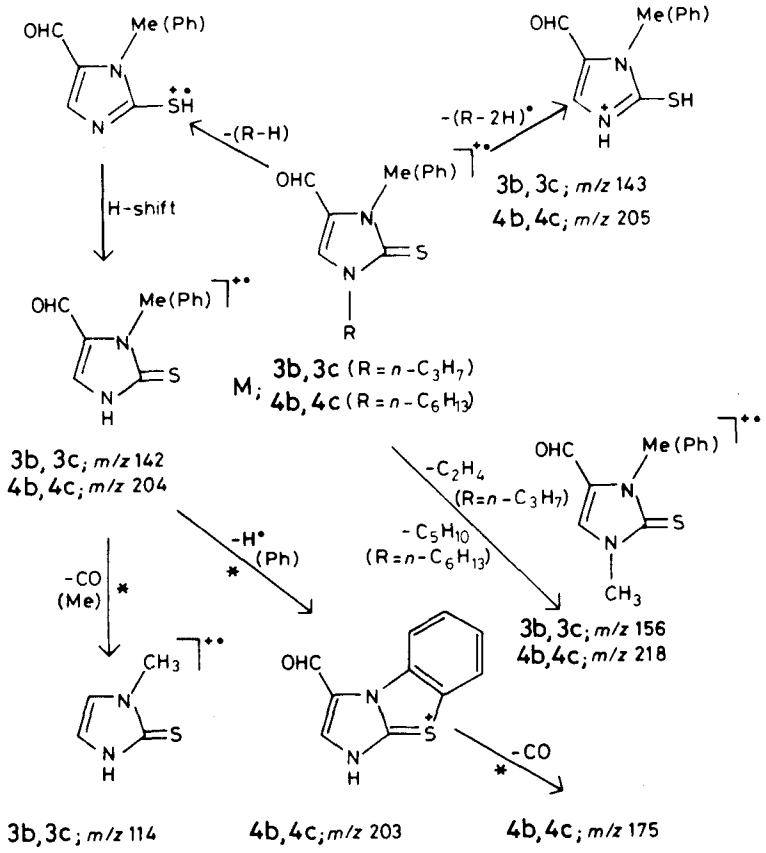
Figure 3. Mass spectra (70 eV) of 4-formyl-1-*n*-hexyl-1,3-dihydro-3-methyl(phenyl)-2*H*-imidazole-2-thiones (**3c** and **4c**).

mentation from the $[M-SH]^+$ ion is found. Therefore, it is resonable to suppose that the loss of SH$^\cdot$ in compounds having long alkylic chains implies an H shift from the alkyl substituent to the sulphur atom, along with the formation of a five-membered ring in the propyl derivatives, and five- and/or six-membered rings in the hexyl derivatives (Scheme 7).

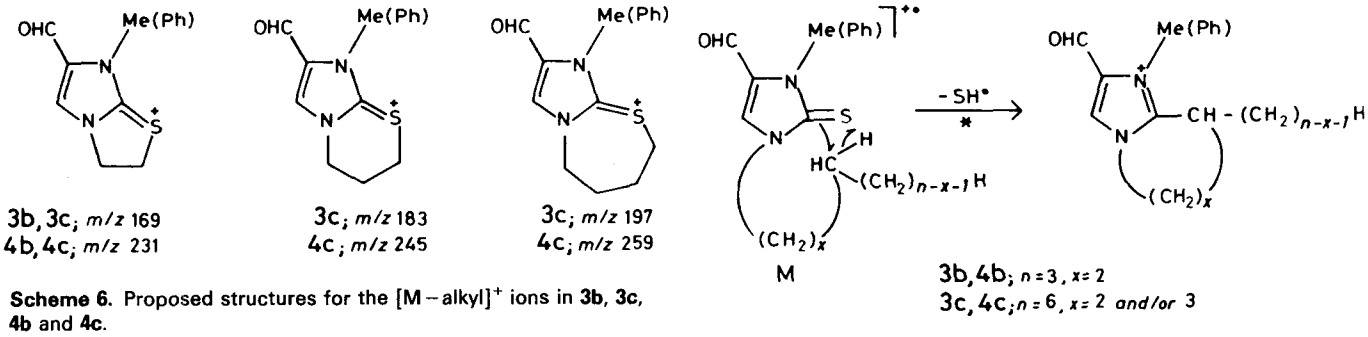
EXPERIMENTAL

The mass spectra were recorded on an MS-30 double-focusing mass spectrometer (AEI Scientific Apparatus), working at an accelerating voltage of 4 kV and a resolution of 1000. Typical source conditions were: electron energy 70 eV, ionization current 0.1 mA and temperature 200 °C. The samples were introduced by a solid probe and heated to 70–200 °C. Accurate mass measurements were carried out at a resolving power of ~10000 with an error within 10 ppm, using a DS-30 computerized data system and PFK as the internal standard. The signals from the second field-free metastable transitions were obtained at a scan rate of 100 s dec^{-1}, an emission current of 0.5 mA and a resolving power of 1000, and were registered on UV recorder. The metastable measurements were correct to within 500 ppm. The exchange of the *N*-bonded hydrogen atoms by deuterium was performed by introducing D_2O into the source via a separate inlet system.

The 4-formyl-1, 3-dihydro-2*H*-imidazole-2-thione (**1**) was prepared from 2-benzylthio-imidazole-4-carboxaldehyde ethyleneacetal by hydrogenolysis with sodium in liquefied ammonia:[11] m.p. 213–214 °C. The 1,3-dihydro-1-phenyl-2*H*-imidazole-2-thione (**2**) was obtained by reaction of aminoacetaldehyde dimethylacetal with phenyl isothiocyanate: m.p. 180–181 °C



Scheme 5. Alkene and alkenyl eliminations in 1-*n*-propyl and 1-*n*-hexyl derivatives **3b**, **3c**, **4b** and **4c**.



Scheme 6. Proposed structures for the $[M-alkyl]^+$ ions in **3b**, **3c**, **4b** and **4c**.

Scheme 7. Proposed mechanism for the loss of SH• from the molecular ion in **3b**, **3c**, **4b** and **4c**.

(literature m.p. 181 °C[12]). The 1-alkyl-4-formyl-1, 3-dihydro-3-methyl(phenyl)-2*H*-imidazole-2-thiones **3** and **4** were synthesized from the corresponding 1,3-disubstituted 4-polyhydroxyalkyl heterocycles by oxidation with sodium metaperiodate:[11] **3a**, m.p. 147–148 °C; **3b**, m.p. 84–85 °C; **3c**, m.p. 78–79 °C; **4a**, m.p. 192–194 °C; **4b**, m.p. 89–91 °C; **4c**, m.p. 73–74 °C.

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