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Mass Spectra of Nine Medicinal Carbamates

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Abstract □ The mass spectra of nine medicinal carbamates (meprobamate, mebutamate, carisoprodol, emylcamate, bethanechol chloride, styramate, hydroxyphenamate, mephenesin carbamate, and methocarbamol) were recorded and examined. Proposed fragmentation pathways were deduced, either by deuterium labeling or by means of accurate mass measurements. The carbamate grouping was expelled at various stages during fragmentation and was lost in a variety of ways.

Keyphrases □ Carbamates—mass spectral characterization of nine drugs □ Meprobamate—mass spectral characterization, fragmentation pathways □ Mebutamate—mass spectral characterization, fragmentation pathways □ Carisoprodol—mass spectral characterization, fragmentation pathways □ Emylcamate—mass spectral characterization, fragmentation pathways □ Bethanechol chloride—mass spectral characterization, fragmentation pathways □ Styramate—mass spectral characterization, fragmentation pathways □ Hydroxyphenamate—mass spectral characterization, fragmentation pathways □ Mephenesin carbamate—mass spectral characterization, fragmentation pathways □ Methocarbamol—mass spectral characterization, fragmentation pathways □ Mass spectroscopy—characterization, nine medicinal carbamates

There are several reports in the literature on the mass spectral behavior of carbamates (1–5), but all of these studies are concerned with *N*-substituted and *N*,*N*-disubstituted carbamates, including many of the carbamate pesticides. Unsubstituted carbamates are employed in medicine as minor tranquilizers and muscle relaxants and for other purposes. Their mass spectra have not been examined in detail.

The study now reported is a continuation of previous investigations (6, 7) on the characterization of medicinal compounds by means of their mass spectra. For this study, nine medicinal carbamates were available. The mass spectrum of each was recorded, and fragmentation pathways were proposed either as a result of deuterium labeling or accurate mass measurements. At the outset, each spectrum was inspected to see whether the chosen carbamates lost the carbamate grouping early in the fragmentation sequence and, if so, whether it was consistently lost as an identifiable molecule or radical such as HNCO or $NH_2COO^{\cdot}$. It soon became clear that the carbamate grouping was expelled at various stages during fragmentation and that it was lost in a variety of ways. However, one diagnostic peak was observed in five of the carbamates. An ion of mass 62 was formed from meprobamate, mebutamate, carisoprodol, mephenesin carbamate, and methocarbamol. An accurate mass measurement in each instance revealed that this ion was $NH_2COOH_2^+$. The elimination of NH_2COOH (or simultaneous expulsion of NH_3 and CO_2) at some stage during the fragmentation sequence was also common to the same five compounds and to emylcamate. The formation of the NH_2COOH molecule is considered to be the result of a hydrogen-transfer mechanism such as that illustrated in the fragmentation of emylcamate.

RESULTS[1] AND DISCUSSION

In the nine carbamates investigated (I–IX), the molecular ion generally either was present in very low abundance or was absent from each spectrum.

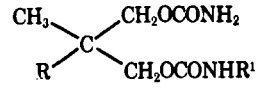
The spectrum of meprobamate (I) (Fig. 1) displayed six fragment ions at *m/e* 144 [146], 114 [115], 101 [102], 96 [96], 84 [84], and 83 [83], which could be useful for characterization purposes. Tetradeuterated meprobamate (I, NH_2, groups replaced with ND_2) gave a spectrum with corresponding deuterated fragment ions. This information, together with the appearance of appropriate metastable ions, permits a rationalization of fragmentation pathways as illustrated in Scheme I. (In all schemes, the mass of a deuterated ion is enclosed in a square bracket, and an asterisk indicates the presence of a supporting metastable ion.)

The chemical structures of mebutamate (II) and carisoprodol (III) are closely related to that of meprobamate. As expected, some of the fragment ions that appear in the spectra of II and III arise in ways similar to those just described for meprobamate. Thus, the spectrum of mebutamate (Fig. 1) possesses abundant ions of *m/e* 158 [160], 128 [129], 110 [110], 115 [116], 97 [97], and 69 [69], which arise in the same manner as the ions *a* and *c–g*, respectively, illustrated in Scheme I.

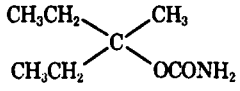
Other abundant ions in the spectrum of mebutamate were located at *m/e* 97, 72, 71, 62, and 55. A rational explanation of their formation is given in Scheme II. In addition, accurate mass measurements were made of all ions and, in this way, the elemental composition of each ion was confirmed as shown. The peak at *m/e* 71 was a doublet,

[1] Mass spectra were recorded by Dr. A. M. Hogg and his associates using an AEI MS-9 mass spectrometer at an ionizing potential of 70 ev. Samples were introduced using the direct probe method. The source temperature was between 75 and 155°, depending on the compound being examined. Accurate mass measurements were carried out by the peak matching method.

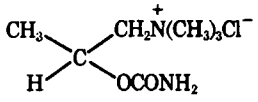
All of the compounds examined were gifts from pharmaceutical firms. All had literature melting points and gave IR spectra consistent with their structures. Each deuterated compound was prepared by boiling, under reflux for 4 hr., a solution of the compound in dioxane containing deuterium oxide and then repeated recrystallization from the same solvent until the O—H and N—H stretching bands in the IR spectra of the unlabeled carbamate were replaced by O—D and N—D stretching bands at longer wavelengths.



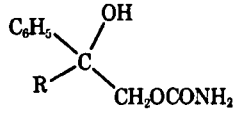
I: meprobamate, R = $CH_3(CH_2)_2$, R_1 = H
II: mebutamate, R = $CH_3CHCH_2CH_3$, R_1 = H
III: carisoprodol, R = $CH_3(CH_2)_2$, R_1 = $CH(CH_3)_2$



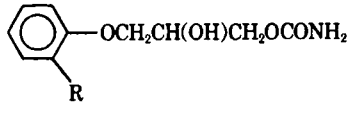
IV: emylcamate



V: bethanechol chloride



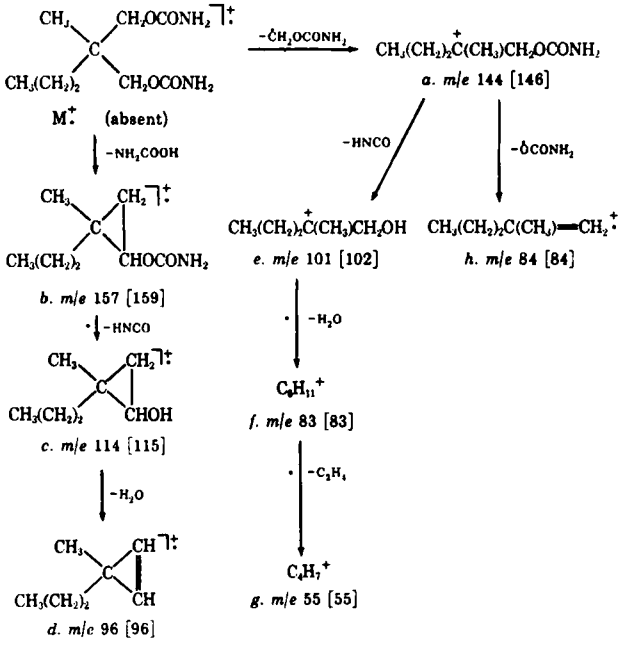
VI: styramate, R = H
VII: hydroxyphenamate, R = CH_2CH_3



VIII: mephenesin carbamate, R = CH_3
IX: methocarbamol, R = OCH_3

C_4H_7O (60%) and C_5H_{11} (40%). Mechanisms for the formation of the latter and for fragment *i* (Scheme II) would be speculative and are not suggested.

The mass spectrum of carisoprodol (III) (Fig. 1) is more complex than the spectra of Compounds I and II. The spectra of III and trideuterated carisoprodol contained fragment ions and appropriate metastable ions which enable the identification of fragments *a*, *c*, *d*, and *f–h* (Scheme I) but, with the exception of the ion *m/e* 55, all of these ions are of low abundance in the spectrum of carisoprodol



Scheme I—Fragmentation of meprobamate

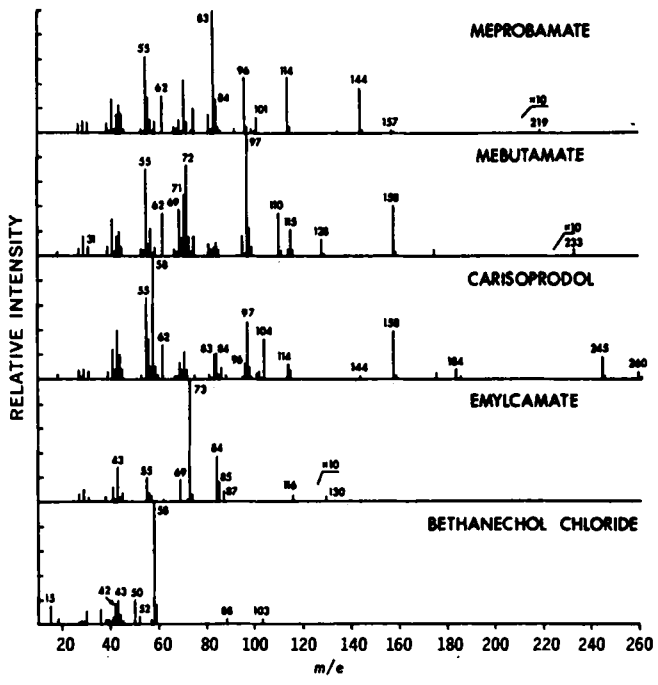
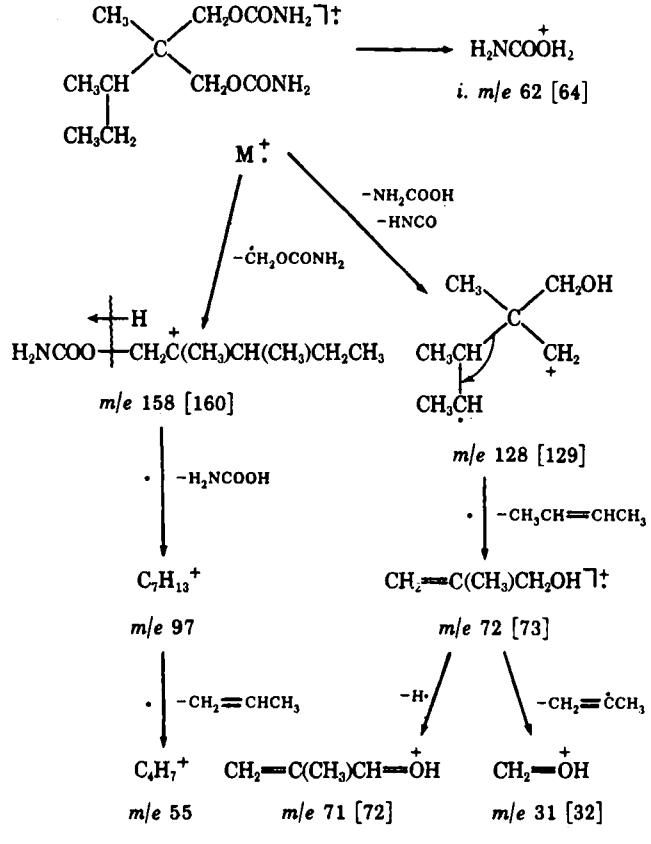


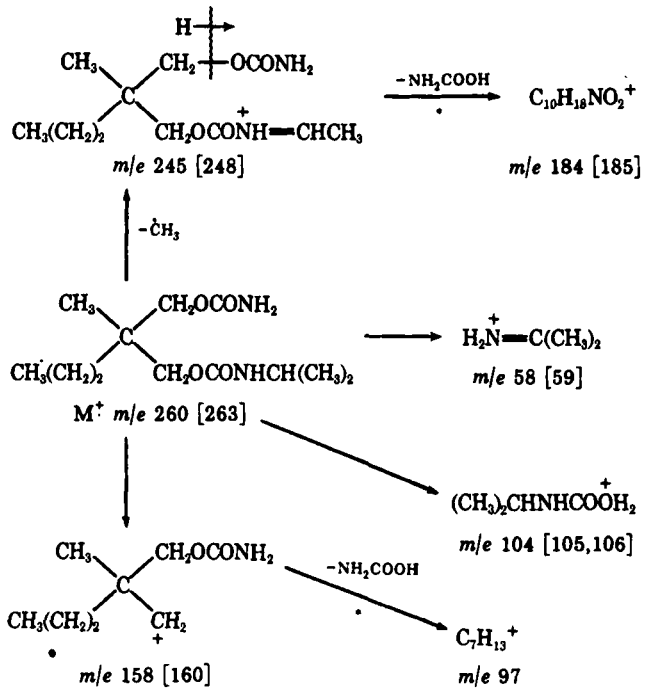
Figure 1—*Mass spectra.*

and of little value for characterization purposes. Fragment ions that are of more value in identification are the molecular ion *m/e* 260; the fragment ions *m/e* 245, 184, and 158, which appear as isolated peaks in the spectrum; and the abundant ions *m/e* 104, 97, and 58 (base peak). Mechanisms for their formation are suggested in Scheme III. Accurate mass measurements of the ions *m/e* 104 and 58 confirmed their elemental compositions.

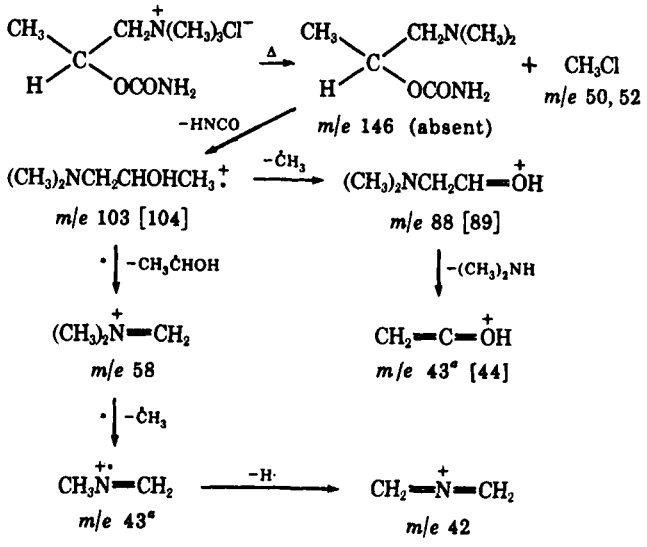
The simplest compound examined was emylcamate (IV), the mass spectrum (Fig. 1) of which lacked a molecular ion; an M−15



Scheme II—Some fragmentations of mebutamate



Scheme III—Some fragmentations of carisoprodol

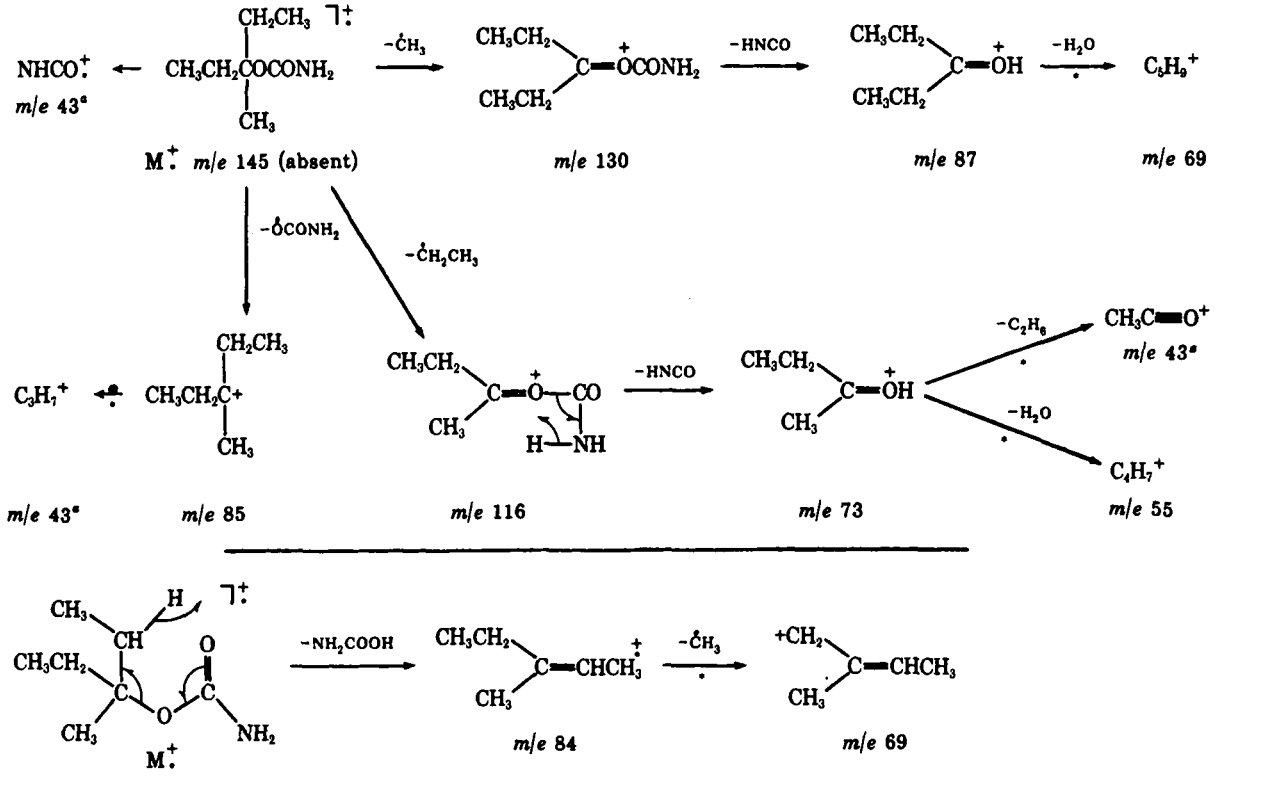


Scheme V—Fragmentation of bethanechol chloride (ᵃdoublet)

ion, due to the loss of a methyl radical from the molecular ion, was less than 1% abundant. A comparison of the spectrum of emylcamate with those of Compounds I–III and with that of *tert*-butyl alcohol (8) permitted the elucidation of the unexceptional fragmentation pathways depicted in Scheme IV. Accurate mass measurements of the ions *m/e* 87, 85, 84, 73, 69, 55, and 43 confirmed elemental compositions in agreement with Scheme IV. The peak, *m/e* 43, was a triplet: C_3H_7 (45%), C_2H_3O (34%), and HNCO (21%).

The quaternary salt, bethanechol chloride (V), also behaved predictably in the mass spectrometer (Fig. 1) by decomposing initially to methyl chloride (*m/e* 50 and 52) and the corresponding tertiary base (9). The molecular ion of the latter was not detected; the ions of greatest mass in the spectrum were located at *m/e* 103 and 88; and although both were of low intensity, their presence is of value in identifying this compound. Additional ions that could assist in the identification of this spectrum are the ion *m/e* 50 (CH_2-^{35}Cl), the base peak (*m/e* 58), and fragments derived from it. Accurate mass measurements of the ions *m/e* 88, 43, and 42 showed them to be $C_4H_{10}NO$, C_2H_3O (90%) and C_3H_8N (10%), and C_2H_4N, respectively. Proposed mechanisms for the formation of fragments in the spectrum of bethanechol chloride are presented in Scheme V.

The formation of the ion C_2H_3O by the expulsion of dimethylamine from the fragment of *m/e* 88 is not supported by a metastable but parallels a similar fragmentation observed (10) in the spectrum of glycerol—*viz.*, $CH_2OHCH{=}O^+H \rightarrow CH_2{=}C{=}O^+H$.



Scheme IV—Fragmentation of emylcamate (ᵃtriplet)

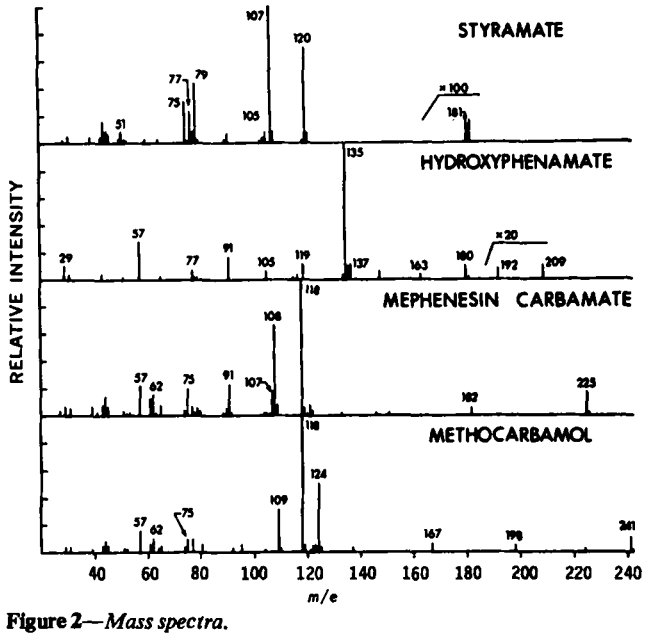
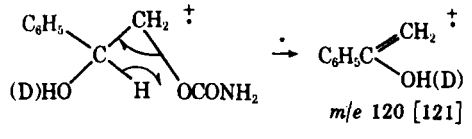


Figure 2—*Mass spectra.*

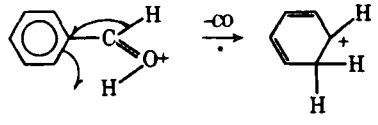
Despite the presence of a stabilizing phenyl substituent, the spectra of styramate (VI) (Fig. 2) and trideuterostyramate did not show molecular ions. The styramate molecule fragmented in the manner typical of a benzyl alcohol derivative (11) by expelling $\cdot CH_2OCONH_2$ and yielding successively ions of *m/e* 107 [108] (base peak, $C_6H_5CH{=}O^+H$), 105 ($C_6H_5C{\equiv}O^+$), 77 ($C_6H_5^+$), and 51 ($C_4H_3^+$). Appropriate metastable ions were present. Other ions of interest were located at *m/e* 120 [121], 79 [80], and 75 [78]. The former was the second most abundant ion in the spectrum. The presence of an appropriate metastable ion (*m/e* 79.6) supported the contention that this *m/e* 120 fragment was derived by expulsion of NH_2COOH from the molecular ion. The location of this fragment at *m/e* 121 in the spectrum of deuterated styramate indicates that a hydrogen atom other than that of the alcohol group is involved in the formation of the NH_2COOH molecule. One appropriate explanation would be the involvement of the H atom of the α-carbon (Scheme VI).

The ions of *m/e* 79 and 75 are readily explained as shown in Schemes VII and VIII.

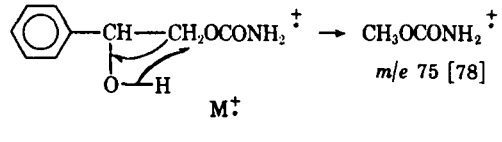
As was observed with styramate, the major fragmentation observed in the spectrum of hydroxyphenamate (VII) (Fig. 2) was the loss of a $\cdot CH_2OCONH_2$ radical and the formation of the base peak at *m/e* 135 [136]. The presence of the ethyl substituent on the α-carbon, however, influenced subsequent fragmentation (Scheme IX), which differed from that observed in the spectrum of styramate.



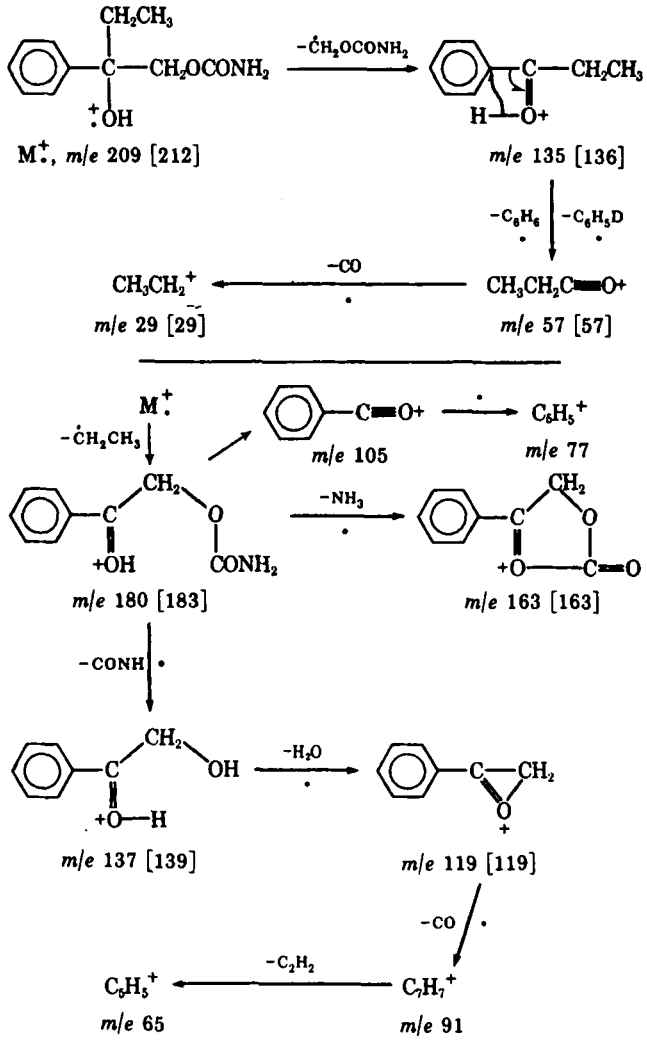
Scheme VI



Scheme VII



Scheme VIII



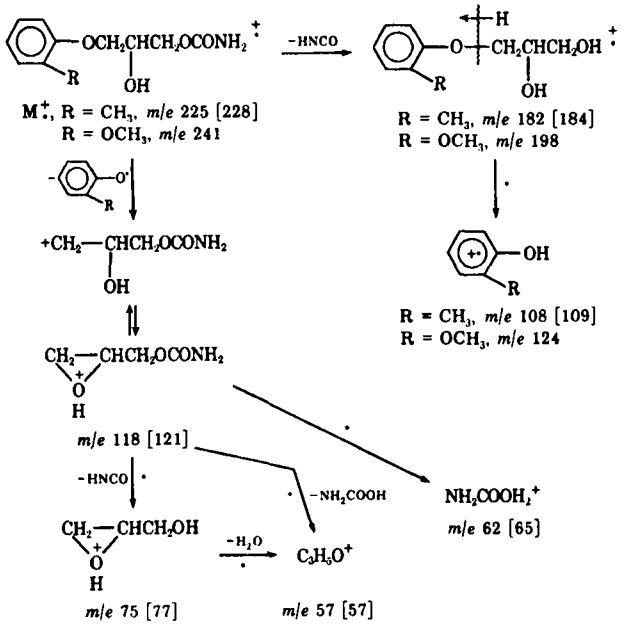
Scheme IX—Fragmentation of hydroxyphenamate

The *m/e* 135 and 57 ions are the most characteristic peaks in the spectrum.

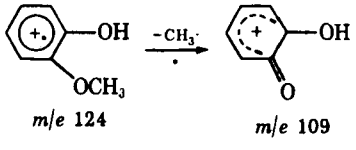
Relatively minor fragmentations which occur with hydroxyphenamate (Scheme IX) are also of some interest and arise as a result of an initial expulsion of an ethyl radical from the molecular ion. An ion of *m/e* 119 is detected in the spectrum of hydroxyphenamate which is absent from the spectrum of styramate. The ion of *m/e* 163 in the spectrum of hydroxyphenamate is of very low abundance (3%) but it is interesting because that same ion is also located at *m/e* 163 in the deuterated compound. Its formation from *m/e* 180 [183], supported by an appropriate metastable ion, must involve the expulsion of the three hydrogen atoms of the NH_2 and OH groups. The proposed mechanism of this unexpected expulsion of an ammonia molecule is illustrated in Scheme IX. An accurate measurement of the ion *m/e* 163 confirmed its elemental analysis as $C_9H_7O_2$.

Mephenesin carbamate and methocarbamol are closely related structures and fragmentation pathways are common to both molecules (spectra given in Fig. 2). Most major ions of value in identification are shown in Scheme X (fragments present in the spectrum of trideuterated mephenesin carbamate are enclosed in parentheses). Additional characteristic ions are located at *m/e* 107 [108] and 91 in the spectrum of mephenesin carbamate; both ions are absent from the spectrum of methocarbamol. The former ion is identified as the hydroxytropylium ion, formed by the expulsion of a hydrogen atom from the *m/e* 108 ion (12). The tropylium ion, *m/e* 91, is presumably formed by expulsion of the ether side chain from either the molecular ion or the fragment *m/e* 182.

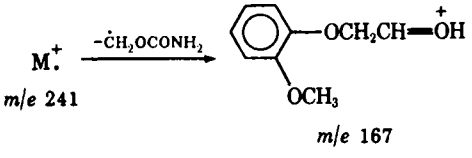
A metastable ion, *m/e* 95.8, supports the postulate that the fragment *m/e* 109 present in the spectrum of methocarbamol (but absent from the spectrum of mephenesin carbamate) is formed as a result



Scheme X—Fragmentations of mephenesin carbamate ($R = CH_3$) and methocarbamol ($R = OCH_3$)



Scheme XI



Scheme XII

of the expulsion of a methyl radical from the ion *m/e* 124 (Scheme XI).

The spectrum of methocarbamol (Fig. 2) also contains a weak, isolated fragment of *m/e* 167. An accurate mass measurement revealed an elemental composition of $C_9H_{11}O_3$, the formation of which is readily explained (Scheme XII).

The present study has shown that medicinal carbamates are readily characterized by means of their mass spectra.

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N-Trisubstituted Methylimidazoles as Antifungal Agents

S. CASADIO▲, A. DONETTI, and G. COPPI

Abstract □ The preparation and the antifungal activity *in vitro* of nine *N*-trisubstituted methylimidazoles related to clotrimazole and of two congeneric compounds, having the 2-pyrrylmethylidenimino and the 2-pyrimidinylamino groups in place of the imidazole nucleus, are presented. Significant activity against six different organisms was found for three compounds. The *in vivo* activity of one selected compound was determined against *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans*. Structure–activity relationships of the tested compounds are also discussed.

Keyphrases □ *N*-Trisubstituted methylimidazoles—synthesis, screened for antifungal activity □ Antifungal agents, potential—*N*-trisubstituted methylimidazoles synthesized and screened □ structure–activity relationships—*N*-trisubstituted methylimidazoles, antifungal activity

Clotrimazole [1-(*o*-chloro-α,α-diphenylbenzyl)imidazole] (1) is a new type of antifungal, which has been reported (2) to possess broad spectrum activity including that of amphotericin B and griseofulvin. The consistent results obtained in patients with severe systemic mycoses and the advantages that this drug