Journal of Chromatography, 126 (1976) 581–589

CHROM. 9474

ALDEHYDE CONDENSATION PRODUCTS AS DERIVATIVES FOR THE VAPOR PHASE ANALYSIS OF BIOGENIC AMINES

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SUMMARY

The mass spectra of six tetrahydroisoquinolines and five tryptolines are surveyed. It is concluded that tryptolines are suitable for analysis of tryptamines, after condensation with aldehydes.

INTRODUCTION

Combined gas chromatography–mass spectrometry (GC–MS) is the method of choice for the sub-microgram analysis of most organic compounds with molecular weights lower than about 1000[1–4]. The technique of selective ion monitoring (SIM) is particularly useful when a high degree of selectivity and/or sensitivity is required[5]. If the instrument is equipped with a suitable data handling system, it is convenient to acquire complete mass spectra during a chromatogram and to reconstruct "single ion" chromatograms later. However, greater sensitivity is attainable if the "single ion" chromatogram is recorded directly[6]. The ultimate sensitivity of the technique may be limited by one or more of several factors. If the sample is not absorbed or destroyed on the gas chromatographic column[7] and if the sample affords sufficient ions to be detected by the mass spectrometer, the most troublesome aspect of selective ion monitoring is background interference. This may derive from the gas chromatograph (O-rings, septa, stationary phases, etc.) or from contaminants in the mass spectrometer (pump oil, previous samples, etc.). These may be distinguished readily if the instrument is equipped with a valve between the gas chromatograph and the mass spectrometer[5]. A background spectrum recorded at maximum amplification at a normal scan speed will indicate the *m/e* values at which major background ions appear. If the sensitivity is increased by widening the focusing slits in the mass spectrometer and increasing the filtering capacity[5], many more minor background ions can be measured. Under such conditions, complete mass spectra cannot be scanned dynamically, but abundances of individual ions may be determined by slowly adjusting the magnet current[5].

In general, maximum sensitivity during SIM is attained under conditions of low background. One approach to the solution of this problem is to use derivatives which render the samples more volatile, thus permitting the use of lower column temperatures. This, in turn, reduces the amount of bleed from the stationary phase,

septum, and O-rings. An alternative approach, the feasibility of which is explored here, is to use derivatives which increase the molecular weight of the sample so that it affords ions of *m/e* values higher than the majority of the background ions. This concept is examined by surveying the utility of mass spectra of aldehyde condensation products of various biogenic amines[8]. The results are also of intrinsic interest since the resulting tetrahydroisoquinolines and tryptolines are of biochemical and clinical significance, yet few of their mass spectra have been examined in detail.

EXPERIMENTAL

Tetrahydroisoquinolines and tryptolines were obtained from commercial sources (Aldrich, Milwaukee, Wisc., U.S.A.; Alfred Bader Chemicals, Milwaukee, Wisc., U.S.A.; K & K Rare and Fine Chemicals, Plainview, N.Y., U.S.A.) or were synthesized as previously described[8] by condensation of the appropriate amine and aldehyde.

Trimethylsilyl (TMS) derivatives were prepared using trimethylsilylimidazole, to produce TMS ethers and esters, or bis(trimethylsilyl)acetamide, which also derivatizes the amino groups.

Low-resolution mass spectra were obtained using the direct insertion probe inlets of LKB 9000 and DuPont 21-490 instruments at 22.5 eV. High-resolution mass spectra were recorded using a CEC 21-110B instrument under similar conditions.

RESULTS AND DISCUSSION

Low-resolution spectra of compounds I–XI are represented in Figs. 1–11. All interpretations are compatible with the high-resolution data.

Tetrahydroisoquinoline (I)

The mass spectrum (Fig. 1) of this compound contains a relatively abundant molecular ion (*m/e* 133) but the base peak (*m/e* 104) is formed by a retro-Diels–Alder rearrangement. Abundant fragment ions are formed also by elimination of up to four

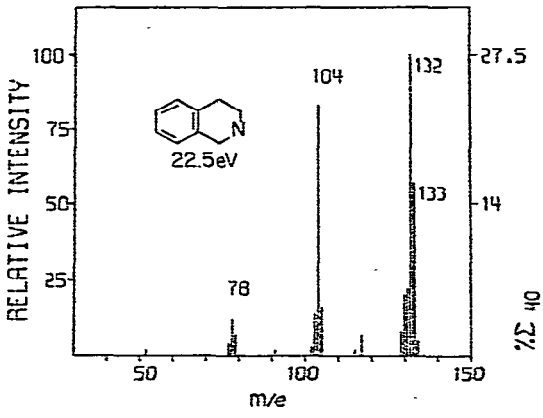

Fig. 1. Mass spectrum (22.5 eV) of tetrahydroisoquinoline (I).

hydrogen atoms from the molecular ion. It should be noted, in particular, that the hydrogen atom at C-1 is readily lost since it is β to both the nitrogen atom and the aromatic ring.

1-Benzyltetrahydroisoquinoline (II)

The mass spectrum (Fig. 2) of this compound further illustrates the propensity for eliminating the substituent at C-1 : this fragmentation mode leads to the formation of the base peak of *m/e* 132. The molecular ion (*m/e* 223) is very weak, but a relatively abundant ion of *m/e* 220 is formed by loss of hydrogen atoms from C-1, C-3, and C-4. The $[M - 5]^+$ ion (*m/e* 218) is apparently formed by condensation of the two aromatic nuclei. There is no ion of *m/e* 194 formed by a retro-Diels–Alder rearrangement.

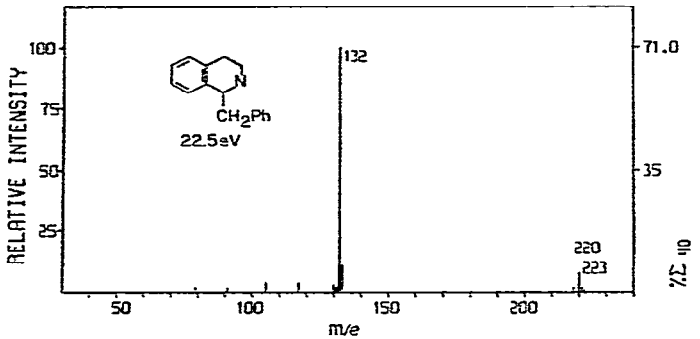

Fig. 2. Mass spectrum (22.5 eV) of 1-benzyltetrahydroisoquinoline (II).

1-Phenyltetrahydroisoquinoline (III)

The cleavage of bonds adjacent to an aromatic nucleus is not commonly observed but, in this compound (see Fig. 3), the substituent at C-1 is sufficiently labile for the ion of *m/e* 132 to become the base peak. This compound also gives rise to an $[M - 5]^+$ ion. The product of a retro-Diels–Alder rearrangement appears at *m/e* 180.0899 ($C_{14}H_{12}$ requires 180.0939). High-resolution data show that all of the other ions in the range *m/e* 151–179 are also formed by cleavage of the heterocyclic ring and elimination of the nitrogen atom. These fragmentations are apparently mediated by the formation of tricyclic products.

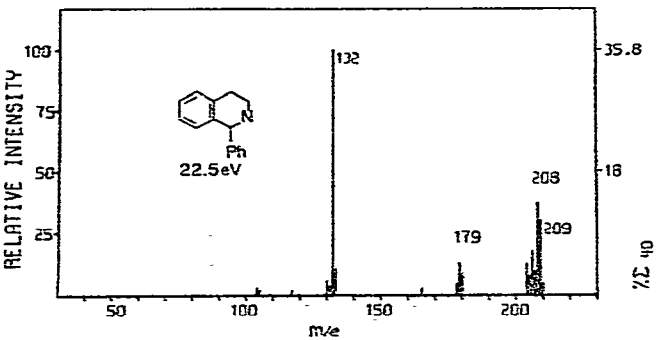

Fig. 3. Mass spectrum (22.5 eV) of 1-phenyltetrahydroisoquinoline (III).

Salsolidine (IV)

All three methyl substituents in this compound are in labile environments, and the spectrum (Fig. 4) is dominated by an $[M - 15]^+$ ion (*m/e* 192). There is a weak ion of *m/e* 178 formed by a retro-Diels–Alder rearrangement. The relatively intense peak of *m/e* 176 is a doublet comprised of $C_{10}H_{10}NO_2$ (calc. 176.0712, obs. 176.0703) and $C_{11}H_{14}NO$ (calc. 176.1076, obs. 176.1051) in the ratio 6:1. The major component is apparently formed by loss of a methoxyl methyl group and methane from the heterocyclic ring of the molecular ion. Both components of this doublet eliminate a molecule of hydrogen to give ions at *m/e* 174 of type $C_{10}H_8NO_2$ (calc. 174.0555, obs. 174.0543) and $C_{11}H_{12}NO$ (calc. 174.0919, obs. 174.0911), respectively, in a ratio of 2:1.

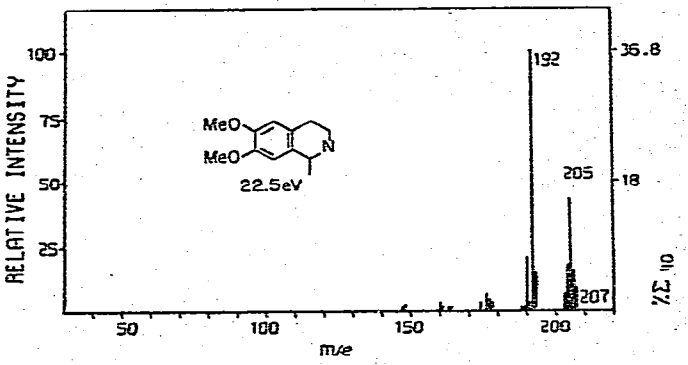

Fig. 4. Mass spectrum (22.5 eV) of salsolidine (IV).

Salsoline (V)

The spectrum (Fig. 5) of this compound exhibits many features of the spectrum of salsolidine. The base peak is of type $[M - 15]^+$ (*m/e* 178), but there is an ion of *m/e* 163 formed by loss of a second methyl group. The accompanying ion of *m/e* 164, formed by a retro-Diels–Alder rearrangement, is less significant. There is,

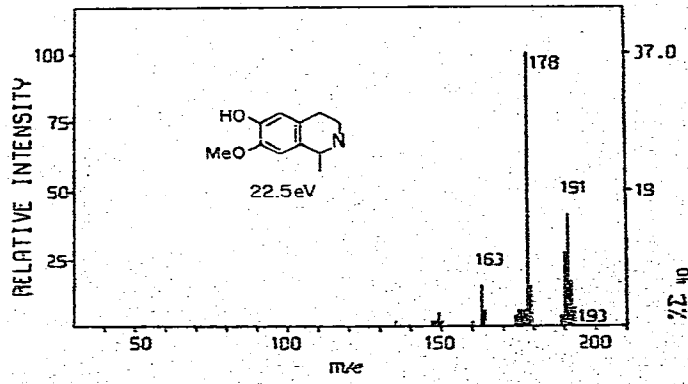

Fig. 5. Mass spectrum (22.5 eV) of salsoline (V).

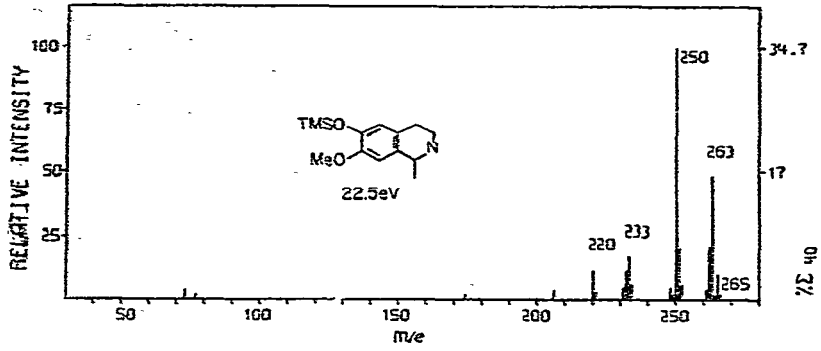

Fig. 6. Mass spectrum (22.5 eV) of salsoline mono-TMS (VI).

however, an ion of *m/e* 149 which may be formed by a retro-Diels–Alder rearrangement of an $[M - 15]^+$ ion, in which a methoxyl methyl group is lost from the molecular ion. Moreover, there is a corresponding ion at *m/e* 220 in the spectrum of the O-trimethylsilyl derivative of salsoline (VI, Fig. 6).

1-Methyltryptoline (VII)

In contrast to the tetrahydroisoquinolines, the molecular ion in the spectrum (Fig. 7) of this and the other tryptolines is more abundant than the accompanying ions formed by loss of one or more hydrogen atoms. As expected, the $[M - 15]^+$ ion (*m/e* 171) is very abundant. The ion of *m/e* 157 is formed by a retro-Diels–Alder rearrangement.

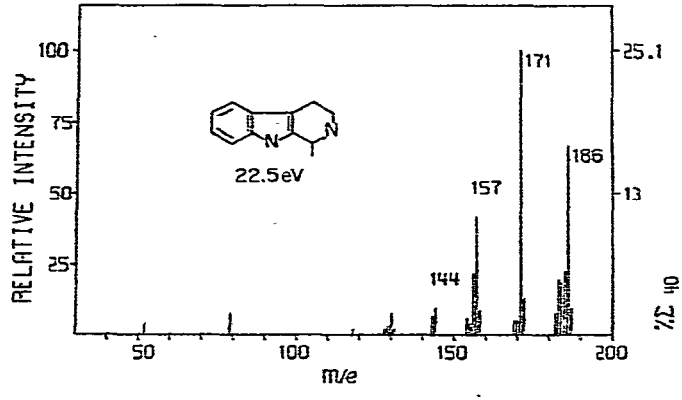

Fig. 7. Mass spectrum (22.5 eV) of 1-methyltryptoline (VII).

Tryptoline-3-carboxylic acid mono-TMS (VIII)

The spectrum (Fig. 8) of this compound contains an abundant molecular ion and only two major fragment ions. Loss of the carboxy-TMS group affords the ion of *m/e* 171, while a retro-Diels–Alder rearrangement yields the ion of *m/e* 143.

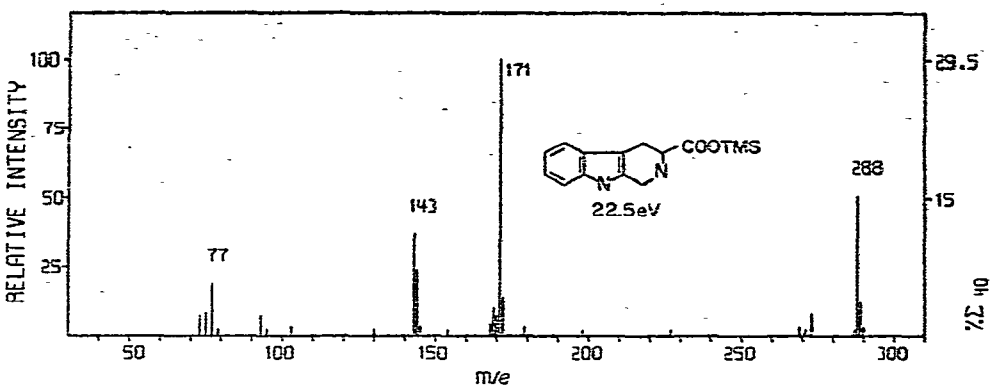

Fig. 8. Mass spectrum (22.5 eV) of tryptoline-3-carboxylic acid mono-TMS (VIII).

Tryptoline-3-carboxylic acid tri-TMS (IX)

In this spectrum (Fig. 9) also, the major ions are the molecular ion (*m/e* 432) and fragment ions due to loss of carboxy-TMS (*m/e* 315) or a retro-Diels–Alder rearrangement (*m/e* 216).

1-(Diethylmethyl)tryptoline-3-carboxylic acid mono-TMS (X)

The alkyl substituent at C-1 is readily lost, so the spectrum (Fig. 10) of this compound is dominated by the ion of *m/e* 287 ($M - C_5H_{11}$). The molecular ion and other fragment ions are relatively weak.

1-Phenyltryptoline-3-carboxylic acid mono-TMS (XI)

There is only a weak ion (*m/e* 287) formed by loss of phenyl group from the molecular ion. Moreover, the product of a retro-Diels–Alder rearrangement (*m/e* 219) is also of very low abundance. The major ions in the spectrum (Fig. 11) are the molecular ion (*m/e* 364) and that formed by loss of carboxy-TMS (*m/e* 247).

Some general observations can be made on the spectra of tetrahydroisoquinolines. In the absence of a substituent at C-1, the molecular ion is relatively abundant and also undergoes a retro-Diels–Alder rearrangement. This type of rearrangement does not afford abundant fragment ions in the spectra of compounds with substituents at C-1. Instead, the molecular ion is generally of low abundance and the substituent at C-1 is readily eliminated. In the case of the 1-phenyl compound, the molecular ion is relatively abundant but the phenyl group is lost, even though this requires a cleavage between a phenyl group and the adjacent carbon atom. The sequential elimination of hydrogen atoms, culminating in the formation of highly conjugated unsaturated polycyclic species is a notable tendency in each of the spectra.

The spectra of the tryptolines, on the other hand, are much simpler. With no substituent at C-1, abundant molecular ions and fragment ions due to loss of the substituent at C-3 and retro-Diels–Alder rearrangements are observed. This rearrangement is suppressed by the presence of a phenyl group at C-1. If an alkyl group is present at C-1 it is readily lost from the molecular ion.

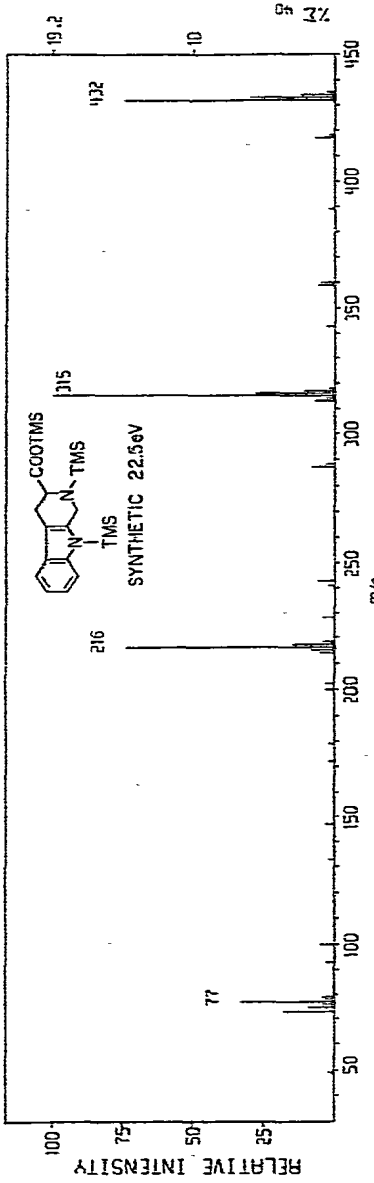

Fig. 9. Mass spectrum (22.5 eV) of tryptoline-3-carboxylic acid tri-TMS (IX).

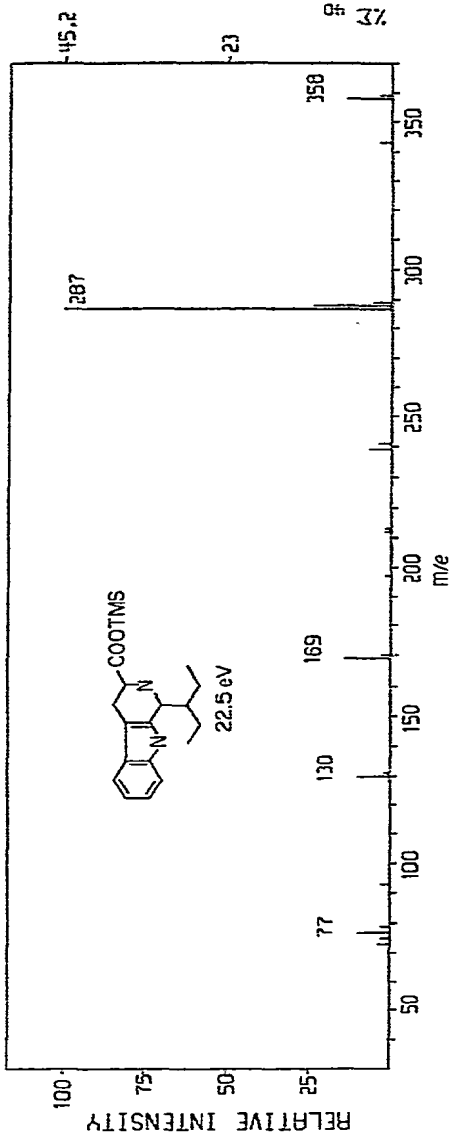

Fig. 10. Mass spectrum (22.5 eV) of 1-(diethylmethyl)tryptoline-3-carboxylic acid mono-TMS (X).

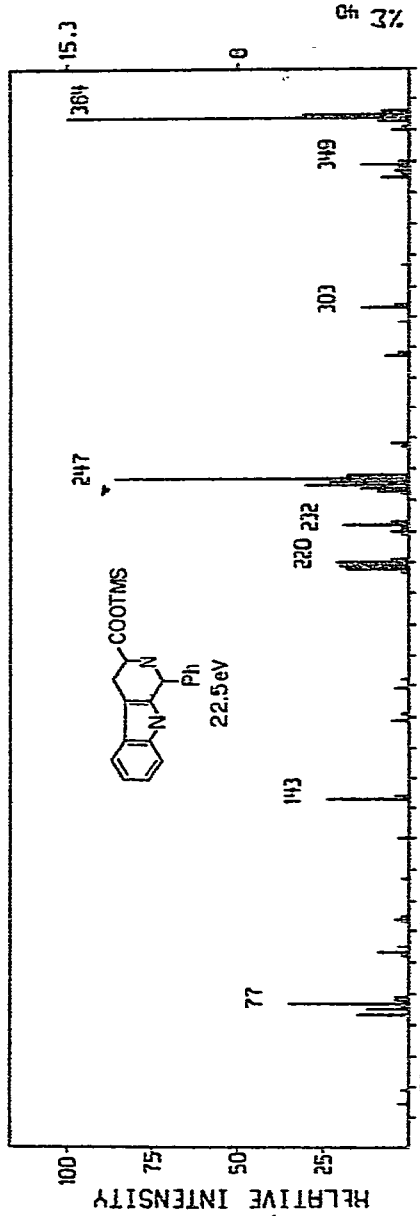

Fig. 11. Mass spectrum (22.5 eV) of 1-phenyltryptoline-3-carboxylic acid mono-TMS (XI).

CONCLUSIONS

The tetrahydroisoquinolines are somewhat disappointing in terms of their potential use as derivatives of β-phenylethylamines for SIM since their molecular ions are usually of low relative abundance. However, ions formed by loss of one or more hydrogen atoms are clearly visible, accounting for 15–20% Σ for IV–VI. In comparison, other derivatives of β-phenylethylamines rarely afford strong molecular ions or related ions formed by loss of hydrogen atoms since the side-chain is so readily cleaved.

In contrast, the tryptolines are more suitable for SIM. With the exception of X, the molecular ions of the compounds studied account for about 15% Σ, and there are only a few (well defined) fragment ions.

The derivatization procedure could be used with a variety of aldehydes, including fluorinated or deuterated compounds, to yield products at almost any *m/e* value, thus avoiding background ions which limit the sensitivity of SIM. Another practical aspect of these compounds is that they may be detected in amine-containing tissues which have been preserved in aldehydes.

ACKNOWLEDGEMENTS

Part of this work was performed at Baylor College of Medicine, where it was partially supported by the National Institutes of Health (GM-13901) and the Robert A. Welch Foundation (Q-125). The work is now being continued with support from the University of Houston. The high-resolution data were kindly supplied by P. Crain.

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