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Mass spectral studies on aryl-substituted *N*-carbamoyl/*N*-thiocarbamoyl narcotine and related compounds

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Positive ion mass spectral fragmentation of new N-carbamoyl/N-thiocarbamoyl derivatives of narcotine and compounds closely related to it are reported and discussed. The techniques used include electron impact (EI), fast-atom bombardment (FAB), matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) and electrospray ionization tandem mass spectrometry (ESI-MS/MS). Prominent peaks in the mass spectra of these compounds appear to involve C-C bond cleavage β to the amine nitrogen with loss of the 4,5-dimethoxy(1*H*)isobenzofuranone moiety from their molecular ions, along with another prominent peak at *m/z* 382. No molecular ion peaks of these compounds were recorded in EI, whereas intense $[M + H]^+$ ion peaks were observed in FAB and ESI spectra. MALDI also yielded $[M + H]^+$ ion peaks in good agreement with FAB and ESI studies.

The mass spectrometry of biologically active heterocyclic systems such as opium isoquinoline alkaloids like narcotine and its *N*-carbamoyl/*N*-thiocarbamoyl derivatives is a subject of current interest. A variety of substituted *N*-carbamoyl or *N*-thiocarbamoyl derivatives of narcotine has been examined by a number of mass spectrometric techniques including electron impact (EI), fast atom bombardment (FAB), matrix-assisted laser desorption/ionization (MALDI) and electrospray with tandem mass spectrometry (ESI-MS/MS). A series of substituted 1,2,3,4-tetrahydroisoquinolines obtained from the cactus alkaloid *pilocereine* has been investigated by EI-MS.[1] It was shown that the molecules exhibited molecular ions of very low intensity (usually <1% of the base peak) and the main fragmentation corresponded to loss of the side chain, adjacent to the nitrogen atom. A similar fragmentation pattern, without any molecular ion formation, has been obtained for narcotine in EI mass spectral studies.[2] These results prompted us to investigate the particle bombardment methods[3–5] and pulsed laser mass spectra[6,7] of these compounds.

Narcotine is a naturally occurring isoquinoline-based alkaloid isolated from *Papaver somniferum*. It is commonly used as an anti-tussive and has recently been shown to exhibit anti-tumor activity; it has been found to act at the level of cytoskeleton proteins to induce apoptosis.[8,9] In the quest for more potent and less cytotoxic anti-tumor agents/drugs, we envisaged synthesis of analogs of noscapine and related compounds having a carbamoyl linkage. In view of their divergent modes of fragmentation, it was considered of interest to study the mass spectra of a series of aryl-substituted *N*-carbamoyl/*N*-thiocarbamoyl narcotine derivatives (compounds **1–11**). Mass measurements with uncertainties of $\pm 0.1\%$ were achieved by MALDI-TOF. Many of the syntheses involve N-demethylation of narcotine followed by its condensation with various aryl isocyanates or aryl isothiocyanates. The compounds were characterized by elemental analysis, IR, PMR (data not shown) and mass spectra.

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EXPERIMENTAL

The electron impact (EI) spectra were obtained using a JEOL JMS-D 300 mass spectrometer. The spectra were run at 70 eV with an emission current of 100 μA. The temperature of the ion source was 200 °C. The solid samples **1–11** were introduced into the mass spectrometer with the direct insertion probe at a temperature of 30 °C. The FAB mass spectra were recorded using a JEOL SX 102/DA-6000 mass spectrometer/data system using argon/xenon (6 kV, 10 mA) as the FAB gas. The accelerating voltage was 10 kV and the spectra were recorded at room temperature. The matrix used was *m*-nitrobenzyl alcohol (NBA) unless otherwise specified, and B/E constant linked scan mass spectra were obtained without gas collision. The reproducibility of spectral patterns was confirmed. The ESI-MS/MS spectra were recorded using a Micromass Quattro II triple-quadruple mass spectrometer. Argon was used as the collision gas and the collision energy was in the range 12–25 eV. The MALDI data were