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In vitro metabolism of zipeprol using hepatic preparations from rabbits

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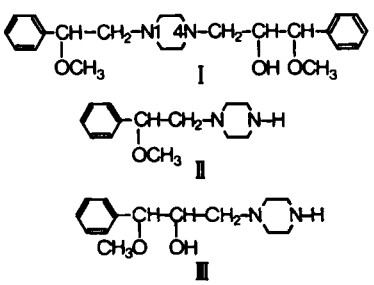
The fate of the antitussive agent zipeprol(I) in man has been studied extensively (Beckett & Achari 1977a, b, c). Its metabolism using 9000 *g* liver homogenates of rabbits fortified with cofactors is now reported.

After zipeprol had been incubated at pH 7·4 for 60 min, an ethereal extract of the alkaline (pH 12) incubation mixture showed four products on thin layer chromatography (silica gel 60; benzene-diethylamine–methanol (80:10:10)) in addition to the substrate (R_F 0·63). Products A(R_F 0·31) and B(R_F 0·22) corresponded with the reference compounds II and III, respectively; these products were examined by mass spectrometry as their NBD derivatives (see later).



I

II

III

The major metabolic product C(R_F 0·48) gave colour reactions similar to zipeprol with Dragendorff and iodoplatinate reagents. This metabolic product was scraped off the plate before spraying, extracted with ether and the concentrated ethereal extract was examined by direct inlet mass spectrometry using an AEI-MS 9 mass spectrometer operated at an ionization potential of 70 eV. The mass spectrum (Fig. 1) indicated that it was the *O*-demethylated product IV (Fig. 2). The spectrum displayed no molecular ion; the abundant ion at *m/z* 249 expelled a molecule of benzaldehyde via the four membered transition state (Fig. 2) to form *m/z* 143. The metastable ion at *m/z* 82·1 supported this direct fragmentation.

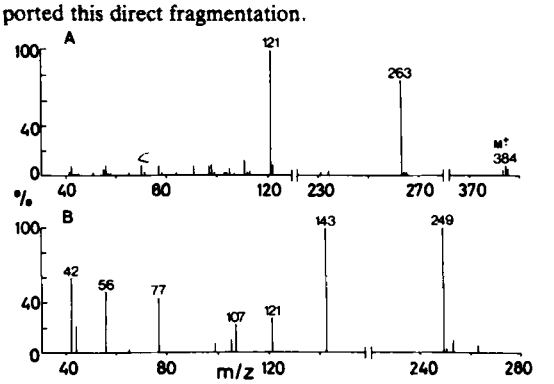


FIG. 1. Direct inlet mass spectra of (A) zipeprol(I) and (B) its metabolic product(IV).

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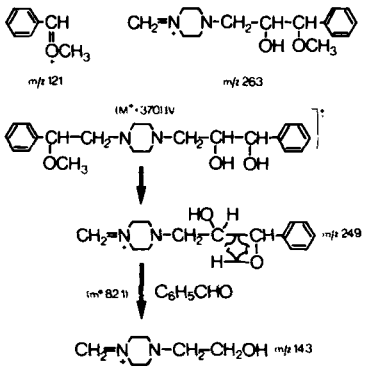

FIG. 2. Characteristic mass ion fragments of zipeprol and its metabolic product(IV).

Treatment of the ethereal extract with NBD chloride (Beckett & Achari 1977c) followed by thin layer chromatographic examination revealed three bright yellow spots on t.l.c. (silica gel 60; chloroform-acetone (70:30)). Two, A (R_F 0·41) and B(R_F 0·22) were identical with the NBD derivatives of compounds II and III respectively. The third, C(R_F 0·27), also present when compound II was further incubated and treated as above, gave a mass spectrum identical to that for the metabolic product obtained in the in vivo study (Beckett & Achari 1977c); it corresponded to that of the NBD derivative of *O*-demethylated compound II.

Thin layer chromatography of the ethereal extract of the incubation mixture at pH 7·4 showed a single spot of the unchanged zipeprol (R_F 0·63): no phenolic products were detected.

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