Identification of a new metabolic product of zipeprol in man

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Zipeprol (I) (Fig. 1), an antitussive agent, is extensively metabolized in man, 1–5% being excreted unchanged in the 24 h urine (Beckett & Achari, 1977b). The two main metabolites are II and III (see Fig. 1) (Beckett & Achari, 1977a). The structure of a third is now reported.

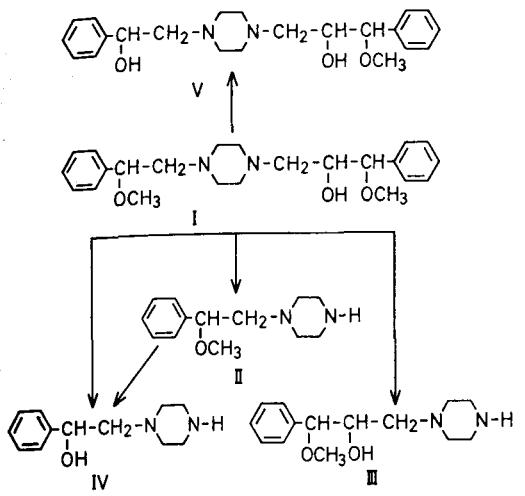

FIG. 1. Proposed metabolic pathways of zipeprol (I) in man.

Preparation of NBD derivative. Details of the administration of zipeprol to volunteers and collection of urine samples have been described by Beckett & Achari (1977b). The urine (10 ml) was made alkaline (pH 12–13) with sodium hydroxide (20%), saturated with sodium chloride and extracted with freshly distilled ether (3 × 15 ml). After concentration to about 1 ml (45°), NBD chloride (7-chloro-4-nitrobenzofurazan) was added (0·2 ml of 0·1% solution in ether), the solvent again evaporated, and the yellow residue was dissolved in chloroform (50 μl).

Thin layer chromatography (t.l.c.) of the above revealed three bright yellow products (silica gel 60; chloroform–acetone 70 : 30) which gave a strong greenish yellow fluorescence under ultraviolet light (350 nm). Products A (R_F 0·48) and B (R_F 0·28) corresponded to the NBD derivatives of compounds II and III, respectively. Product C (R_F 0·35) was eluted from the t.l.c. plate with methanol, and examined by direct inlet mass spectrometry using an AEI-MS9 (70 eV: 160°).

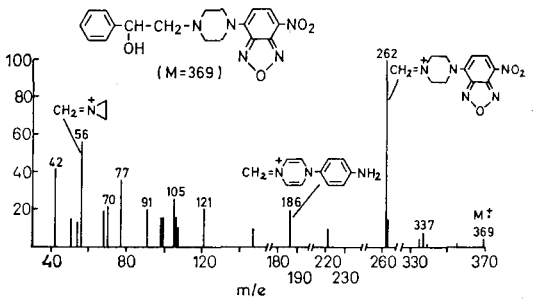

FIG. 2. Direct inlet mass spectrum of the NBD derivative of product C.

Product C was assigned the structure IV (see Fig. 1) for the following reasons.

1. It reacted with NBD chloride to give a strong yellow complex thus indicating a primary or secondary amine function.
2. Product C could be identified after a dose of compound II, but not after compound III.
3. The mass spectrum was interpreted on the basis of Fig. 2.

Mass measurements were carried for *m/e* 262 ($C_{11}H_{12}N_5O_3$: calculated, 262·0940; measured, 262·0940) and *m/e* 186 ($C_{11}H_{12}N_3$: calculated, 186·1031; measured, 186·1025) ions: a metastable (*m/e* 132·0) was observed between the *m/e* 262 and *m/e* 186 fragments.

The above findings also suggest that one of the metabolic products of zipeprol may be the *O*-demethylated product V (see Fig. 1).

We thank CERM, Riom (France) for supplying the compounds I, II and III and Dr J. F. Harper of Advisory Services (Clinical & General) Ltd. for organizing the volunteers. R.A. also thanks Chelsea College for a studentship.

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June 14, 1977

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