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In vitro metabolism in the rabbit of desipramine and nortriptyline to yield carboxylic acids

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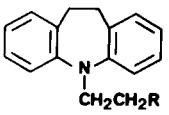
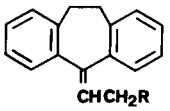
Among reports on the metabolism of the tricyclic antidepressant drugs few have referred to α-carbon oxidation resulting in deamination of the aminopropyl side chain (see for example, Hucker 1962; Crammer et al 1969; Facino et al 1970). Incubation of desipramine (Ia) and nortriptyline (IIa) with fortified 9000 *g* fraction rabbit liver homogenates (see Beckett & Navas 1978) has now been shown to yield carboxylic acids.

Ethereal extracts of the liver homogenates were examined by preparative t.l.c. on glass plates (20 × 20 cm) spread to a thickness of 0.5 mm with a mixture of silica gel GF_{254} (Merck) and water (1:2), dried at room temperature (20 °C) for 15–20 min and then heated for 1·5 h at 115 °C. The plates were pre-washed by development with the solvent system (chloroform–methanol 9:1); solvents were distilled before use. After development, the required bands were visualized at 254 nm.





Ia R=CH_2NHCH_3
Ib R=COOH
Ic R=$COOCH_3$

IIa R=CH_2NHCH_3
IIb R=COOH
IIc R=$COOCH_3$

The metabolic product from desipramine (Ia: R_F 0·18) had R_F 0·35. The direct inlet mass spectrum (recorded on a VG Micromass 12F mass spectrometer, 70eV), of this metabolite showed fragment ions typical of 5-alkyliminodibenzyl derivatives (Frigerio et al 1972; Belvedere et al 1975; Hutt 1979), e.g. *m/z* 208 (base peak), 193 (38% relative intensity; arising from 208 by elimination of a methyl radical) and 194 (21) in addition to ions *m/z* 267 (40), 119 (14), 118 (12), 73 (42), 60 (40). Mass measurement of the molecular ion showed an accurate mass 267·1242 (obtained using an AEI MS-9 mass spectrometer) in agreement with $C_{17}H_{17}NO_2$, i.e. the product corresponding to a carboxylic acid resulting from α-carbon oxidation and subsequent deamination of the aminopropyl side chain and then oxidation of the resulting aldehyde.

The mass spectrum of the methyl ester (Ic), showed a molecular ion at *m/z* 281 (21) with fragments at *m/z* 222 (10) and 208 (100) corresponding to the loss of CO_2CH_3 and $CH_2CO_2CH_3$ respectively.

Thus the metabolite is 3-(10,11-dihydro-5H-dibenz[b,f]azepin-5-yl) propionic acid (Ib).

The metabolism of nortriptyline (IIa), under the same conditions as desipramine (Ia), also yielded a carboxylic acid (IIb), in a manner analogous to the above. With the same t.l.c. system, this had R_F 0·41 (nortriptyline, IIa: R_F 0·17).

Direct inlet mass spectrometry of the metabolite yielded a molecular ion *m/z* 264 (76; accurate mass 264·1132 corresponding to $C_{18}H_{16}O_2$) with additional ions 265 (14), 219 (44), 206 (20), 205 (100), 204 (48), 203 (26), 191 (43). The methyl ester (IIc) showed fragment ions at *m/z* 278 (26, M^+), 219 (60), 217 (20), 205 (100), 204 (48), 203 (40), 202 (30), 192 (16), 191 (78). The metabolic product is thus 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene) propanoic acid (IIb).

The above results suggest that deamination in the rabbit is a route in the metabolism of the tricyclic antidepressant drugs.

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