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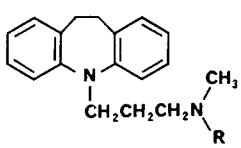
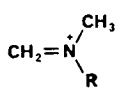
LETTERS TO THE EDITOR

Metabolism of amitriptyline, nortriptyline, imipramine and desipramine to yield hydroxylamines

It has already been reported that many aralkylamine drugs possessing the $-CHCH_3-$ group next to a secondary or primary amine are oxidized metabolically to yield hydroxylamines; tertiary amines on the same structures which undergo metabolic dealkylation also yield hydroxylamines upon metabolism (Beckett, 1971; Beckett, Van Dyke & others, 1971; Beckett & Al-Sarraj, 1972; Beckett, Coutts & Ogunbona, 1973).

Metabolism of drugs containing tertiary and secondary amines possessing a $-CH_2-$ group adjacent to the basic centre is now shown to yield hydroxylamines; amitriptyline (Ia) nortriptyline (Ib), imipramine (IIa) and desipramine (IIb) were chosen as examples.





I a, R = CH_3
b, R = H
c, R = OH

II a, R = CH_3
b, R = H
c, R = OH

III a, R = CH_3
b, R = H
c, R = OH

Incubation of (Ia) or (Ib) with liver fractions i.e. 10 000 *g* fractions, microsomes or 140 000 *g* soluble fraction of rabbits or guinea-pigs gave the hydroxylamine (Ic) while IIa and IIb gave the hydroxylamine IIc; mitochondria gave the same reaction with Ib and IIb but not with Ia and IIa.

After incubation of aqueous solutions of the four drugs at pH 7·4 for 40 min with the above liver fractions appropriately fortified with co-factors, the ether extracts of the mixtures were chromatographed using a g.l.c. system OV 17, 1·5% on Gas-Chrom Q(100–120), 1 m glass column oven temp. 175°, nitrogen (carrier gas) 20, Air 20 and H_2 20 p.s.i. In addition to peaks for Ia (Rt 6·9 min) and Ib (Rt 8·4 min) (*N*-acetyl, 9·5 min at 210°) after the metabolism of Ia, or for unchanged drug after the metabolism of Ib, there was observed another peak of Rt 9·6 min (after t.l.c. separation—see later) of height relative to the above to indicate the presence of a major metabolite; the additional peak was absent when the ethereal solution was reduced with $TiCl_3$/HCl before chromatography.

When the ethereal extracts of the mixtures after metabolism of Ia were chromatographed by t.l.c. on silica gel using chloroform: methanol (9·1), spots corresponding to that of Ia (R_F 0·42) and Ib (R_F 0·15) were observed. In addition, after incubation of both Ia and Ib, there was a spot R_F value 0·75 which gave a black spot with ammoniacal silver nitrate, a red spot with triphenyltetrazolium chloride reagent and a blue spot with sodium aminoprusside reagent.

The area corresponding to the additional spot was scraped off, extracted with ether and the solution concentrated and subjected to g.l.c. and to mass spectrometry and to reduction with $TiCl_3$/HCl. Mass spectrometry gave the fragment IIIc m/e 60 characteristic of secondary hydroxylamines possessing a $N-CH_3$ group; Ia and Ib on the other hand gave the characteristic fragment IIa m/e 58 and IIIc m/e 44 respectively (see Beckett & Essien 1973).

The above evidence demonstrated that the new metabolite of Ia and Ib is the hydroxylamine Ic.

The metabolism of imipramine IIa and desipramine IIb also gave a new metabolite shown to be the hydroxylamine IIc in a manner analogous to the above. G.l.c. gave the following results: imipramine IIa (Rt 8·4 min), IIb (Rt 10·8 min) (*N*-acetyl 11·9 min at 210°), the hydroxylamine IIc (Rt 9·3 min). T.l.c. gave IIa (R_F 0·37), IIb (R_F 0·14), IIc (R_F 0·8); the spots for the latter compound gave colours identical to those reported for Ic above. Ethereal extracts of the scraped area of IIc were reduced by $TiCl_3$/HCl to yield the secondary amine IIb. Mass spectrometry of IIc gave the characteristic fragment IIIc *m/e* 60 instead of IIIa *m/e* 58 or IIIb *m/e* 44 from the tertiary amine IIa and the secondary amine IIb respectively.

The metabolism of Ia and Ib also yielded a small amount of the hydroxylamine (R_F 0·68) of the primary amine desmethylnortriptyline (R_F 0·18) and the metabolism of IIa and IIb also gave minor amounts of the hydroxylamine (R_F 0·60) of the primary amine, desdimethylimipramine (R_F 0·16).

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