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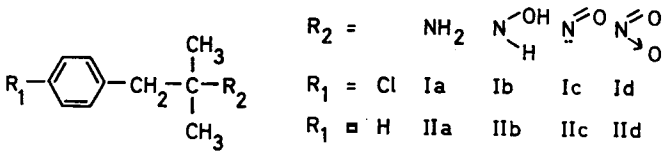
COMMUNICATIONS

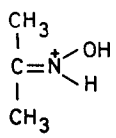
Metabolism of chlorphentermine and phentermine in man to yield hydroxylamino, *C*-nitroso- and nitro-compounds

N-Oxidation is an important metabolic route *in vitro* and *in vivo* in animals and man (Bickell, 1969, 1971; Beckett, 1971; Jenner, 1971; Beckett, Vaughan & Essien, 1972; Gorrod, 1973): tertiary amines yield *N*-oxides; secondary amines yield hydroxylamines which are readily changed to nitrones, if they possess at least one hydrogen atom on the α-carbon (Beckett, Coutts & Ogunbona, 1973), while primary amines give hydroxylamines that are readily converted to oximes (Beckett & Al-Sarraj, 1972). Some hydroxylamines are concentrated in red blood cells (Beckett & Essien, 1973).

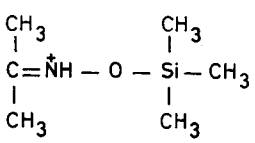
If there is no hydrogen atom on the α-carbon of primary amines, the metabolically derived hydroxylamines will probably form *C*-nitroso- and nitro-compounds on further enzymatic or non-enzymatic oxidation; the presence of these compounds in man given chlorphentermine and phentermine is now shown.

After an oral dose of chlorphentermine (Ia) in man, g.l.c. analysis of ethereal extracts of neutral (pH 7·4) urine on Carbowax 20M 7·5% (Column A, N_2 26 lb inch^{-2}) or OV-17 3% (Column B, N_2 15 lb inch^{-2}) gave peaks corresponding to the nitroso compound Ic (Column A, 130°, Rt 6·8 min), the nitro compound Id (Column B, 160°, Rt 11·6 min) and the hydroxylamine Ib [identified as the trimethylsilyl and acetyl derivatives on a glass column (SE-301 3% plus Triton X-305 0·01% N_2





III



IV

10 lb inch^{-2}), TMS derivative Rt 12·6 min at 100° and acetyl derivative Rt 12 min at 130°]. Additional Ib was liberated upon enzymic hydrolysis (sulphatase-β-glucuronidase mixture) of the urine. G.l.c.-m.s. of the hydroxylamine (Ib) and its TMS derivative gave characteristic ions at *m/e* 74 (III) and 146 (IV) respectively; of Id, a molecular ion at *m/e* 213 but no characteristic ions for Ic and Id. Oxidation of the remaining aqueous layer with $K_2Cr_2O_7$ or $KMnO_4$, or re-extraction of the urine at alkaline pH, led to the recovery of an additional amount of Id. About 10% of the dose (65 mg) of chlorphentermine (Ia, as HCl) was obtained from human urine as *N*-oxidation products.

Extraction of plasma or red blood cells from blood samples collected up to 6 h after an oral dose of chlorphentermine (65 mg) at pH 7·4 gave Id; subsequent oxidation of the extracted aqueous phases gave additional Id indicating the presence of *N*-oxidation products of metabolism, probably conjugated Ib.

Likewise phentermine (IIa, 25 mg as HCl) in man gave in ethereal extracts of neutral urine the hydroxylamine IIb (Column A, 150°, Rt 12·6 min and B, 100°, Rt 8·4 min) and the nitroso IIc (Column A, 100°, Rt 7·8 min). The nitro IId (Column A, 150°, Rt 8·8 min and B, 100°, Rt 12·1 min) was not detected unless the urine was extracted under alkaline conditions or oxidized chemically. Less than 5% of the dose was obtained from the urine as *N*-oxidation products.

The above compounds were identified by comparison with authentic compounds synthesized by unequivocal routes and characterized chemically; synthetic and metabolically produced materials behaved similarly.

These products of metabolism may have significance in the toxicology of the two drugs especially for chlorphentermine (Ia, Lüllmann, Rossen & Seiler, 1973) which is used at higher therapeutic doses, has a longer biological half-life (Beckett & Brookes, 1971) and is metabolized to a greater extent than phentermine by the *N*-oxidation route.

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Department of Pharmacy,
Chelsea College (University of London),
Manresa Road,
London SW3 6LX, U.K.

A. H. BECKETT
P. M. BÉLANGER

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