Pethidine *N*-oxide: a metabolite in human urine

N-Oxidation is a major route of tertiary amine metabolism. Recently, methadone *N*-oxide was characterized as a metabolite of methadone (Beckett, Mitchard & Shihab, 1971) and later identified in human urine after a therapeutic dose (Beckett, Vaughan & Essien, 1972). We have now isolated and identified the *N*-oxide metabolite of pethidine from human urine. Urine was collected from patients who had received intramuscular pethidine (100 mg) and the norpethidine and pethidine *N*-oxide metabolites were characterized by chromatographic and spectroscopic techniques.

Thin layer chromatography (silica; benzene–methanol–diethylamine, 75:15:10) of a concentrated chloroform extract of urine gave three spots having R_F values of 0·65, 0·55 and 0·35 which correspond to values obtained for authentic samples of pethidine, norpethidine and pethidine *N*-oxide respectively. T.l.c. of a concentrated chloroform extract of urine after reduction with $TiCl_3$/HCl gave only two spots corresponding to pethidine and norpethidine. The t.l.c. spot obtained from urine corresponding to the *N*-oxide was collected and extracted with water. T.l.c. of an ethereal extract of the solution after reductive dealkylation with sulphur dioxide gave two spots corresponding to pethidine and norpethidine.

Gas liquid chromatography: urine made alkaline was completely extracted with ether and the concentrated extract was chromatographed on Apiezon (10%) + KOH (10%) to give two peaks having retention times of 7·4 and 8·4 min which corresponded to pethidine and norpethidine respectively. Chromatography of a second ethereal extract obtained after $TiCl_3$/HCl reduction of the extracted urine gave only one peak with a retention time corresponding to that of pethidine.

The mass spectra (220° and 70 eV) of pethidine, authentic pethidine *N*-oxide and pethidine *N*-oxide isolated from urine were identical presumably due to thermal elimination of the oxygen atom from the *N*-oxide. There was no evidence in a mass spectrum of a chloroform solution of the t.l.c. *N*-oxide spot from urine to suggest the presence of an *N*-dimethyl quaternary compound.

The nmr spectrum obtained from a CD_3Cl extract of the t.l.c. *N*-oxide spot from urine was identical with that of an authentic sample of pethidine *N*-oxide; both showed a characteristic down field shift of the N-CH_3 from τ 7·7 of pethidine base to τ 6·4 due to the inductive influence of the oxygen atom. Protonation of the N-CH_3 as in pethidine hydrochloride gave a singlet corresponding to the *N*-methyl at τ 7·2.

Polarography of a solution of the t.l.c. *N*-oxide spot from urine in Walpole's acetate buffer pH 5·0 gave a reduction peak potential of −1·25 V which corresponded to the value obtained for pethidine *N*-oxide.

Pethidine *N*-oxide has been identified in the urine of five patients receiving intramuscular pethidine and is therefore assumed to be a normal metabolite of pethidine in man.

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