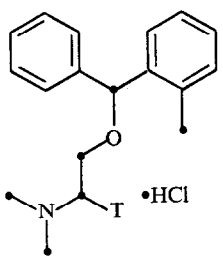
Biochemical Pharmacology, Vol. 16, pp. 1847–1848. Pergamon Press Ltd. 1967. Printed in Great Britain

SHORT COMMUNICATIONS

Evidence for side-chain degradation of orphenadrine HCl in the rat

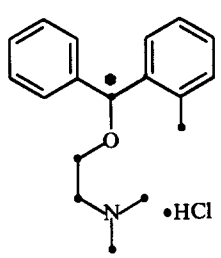
(*Received* 24 *April* 1967; *accepted* 18 *May* 1967)

DURING investigations into the metabolic fate of orphenadrine hydrochloride in the rat, which were an extension of previously published work on the same subject,[1] use was made of orphenadrine hydrochloride, labelled with tritium in the side chain as shown in compound I. The synthesis has been described elsewhere.[2] When the urine, collected after administration of compound I to rats (10 mg/kg, or.), was distilled it was found that amounts of radioactivity came over. When the urinary distillates were collected in small fractions of equal volume (in general about ten) it was observed that after a peak radioactivity in the first fractions a stable level of radioactivity was maintained throughout the other fractions. The peak of radioactivity in the first fractions is indicative for a volatile



I

radioactive product which is easily carried over by the water vapour (steam distillation effect); on the other hand, the constant radioactivity level found in the later fractions can only be related to a radioactive product with distillation characteristics very similar to those of water, the most likely candidate being tritiated water. This assumption was corroborated by the fact that in a second experiment, in which ^{14}C-labelled orphenadrine hydrochloride (II) was used, the peak radioactivity in the first distillation fractions was observed again, but in the later fractions, levels, if found at all, were not constant and very low.



II

The amounts of tritium radioactivity distilling at a constant rate could easily be related to the administered dose as well as to the amounts excreted in the respective urinary samples, which is shown in Table 1.

TABLE 1. RADIOACTIVE WATER IN URINE SAMPLES FROM RATS, COLLECTED OVER SUCCESSIVE TIME INTERVALS AFTER ORAL ADMINISTRATION OF 10 MG/KG OF ORPHENADRINE-^{3}H HCl (I)

Time interval of collection in hr	Radioactivity present as water (Each value represents the mean of two rats) percentage of administered dose	percentage of total radioactivity in urine
0– 8	0·06	0·76
8–24	0·20	0·76
24–48	0·38	15·38
48–72	0·32	46·38

From these figures it can be concluded that a volatile radioactive product is involved, the biological half-life of which amounts to several days. Since this is in agreement with that reported in the literature for tritiated water in the rat,[3] little doubt would remain that tritiated water is actually present. The question arises of how it is formed. Chemical instability of the label is unlikely; on theoretical grounds the tritium atom can be regarded as being bound very stable. The alternative explanation is a metabolic attack on the side chain, setting free the label. A possibility might be that *N,N*-didemethyl orphenadrine, one of the metabolites of orphenadrine in the rat,[2] would be subject to an oxidative deamination. This is consistent with the literature on related compounds such as amitriptyline[4] and chlorpromazine[5] for which an oxidative deamination *in vivo* has been proposed on the ground of the structure of metabolites found. Moreover, a reaction starting from *N,N*-didemethyl orphenadrine would explain the quantitatively minor importance of this side-chain degradation, which will be limited by the concentration of the intermediate metabolite, itself formed in small amounts only.

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Biochemical Pharmacology Vol. 16, pp. 1848–1852. Pergamon Press Ltd. 1967. Printed in Great Britain

Effects of halothane, trichloroethylene, pentobarbitone and thiopentone on amino acid transport in the perfused rat liver

(*Received* 28 *March* 1967; *accepted* 3 *May* 1967)

EVIDENCE[1, 2] has recently been presented that the liver plays an important role in the regulation of blood amino acid levels. Since various anaesthetics have been found to have effects on membrane functions of liver cells,[3] experiments were conducted to find whether the anaesthetics also affect amino acid transport in the perfused rat liver.

METHODS

The isolated, perfused rat liver preparation used in this work was similar to that described by Fisher and Kerly,[4] but adapted for the use of Krebs–Ringer bicarbonate buffer instead of rat blood as perfusion medium. The method will be described in full elsewhere.[5]