A new metabolite of amylobarbitone: 5-(3′-carboxy-butyl)-5-ethylbarbituric acid

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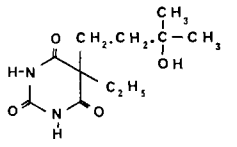
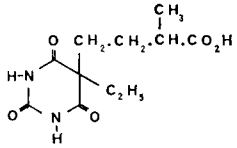
Although the human metabolism of amylobarbitone has been investigated on a number of occasions (e.g. Maynert, 1965; Draffan, Clare & Williams, 1973) the only reported urinary metabolite‡ is the 3′-hydroxy derivative (I), which accounts for around 50% of the ingested dose.



I



II

A healthy male volunteer took orally sodium amylobarbitone (200 mg capsule, *Eli Lilly*); batches of urine were extracted with ethyl acetate, using barbitone and 2′-hydroxyethylethylbarbituric acid as internal standards as previously described (Gilbert & Powell, 1977), methylated and examined on the Finnigan g.c.–m.s. instrument using the OV 210 column at 200°. In addition to peaks in the *m/e* 169 output at appropriate retention times for amylobarbitone, 3′-hydroxyamylobarbitone, and the two internal standards, a fifth peak consistently appeared at relative retention time 3·35 (amylobarbitone = 1·00). The peak was present in 15 × 8 h batches of urine, and its area declined at a similar rate to the unchanged drug and its metabolite, strongly suggesting the peak to be derived from a bona fide metabolite of amylobarbitone. Other mass spectral fragments present at the same retention time included *m/e* 97, 112, 126 and 184, all of which are characteristic of methylated 5-ethyl barbiturates. The partial mass spectrum, together with the retention data, were consistent with the proposal that the new metabolite could be the product of ω-hydroxylation of the 3′-methylbutyl side-chain.

Meanwhile, further evidence was obtained from the analysis of forensic samples of urine for the presence of barbiturate metabolites. Analyses were carried out on a V.G. Micromass 12F g.c.-m.s. instrument, using a 6 ft × ¼ in 3% OV-17 column at 200°. Components of interest in the methylated, acid/ether extracts were examined by g.c.-m.s. employing both electron impact (e.i.) and isobutane chemical ionization (c.i.) techniques.

In an amylobarbitone overdose case the extract was found to contain, in addition to the *NN′*-dimethyl derivatives of amylobarbitone and (I), a peak at a relative retention time 3·6 (*NN′*-dimethyl amylobarbitone = 1). The c.i. spectrum of this component was highly characteristic of the *NN′*-dimethyl derivative of a 5-ethyl substituted barbiturate. The c.i. spectrum had a base peak at *m/e* 299 which is consistent with a quasi-molecular ion (MH^+) derived from the methyl ester of the *NN′*-dimethyl derivative of (II). Further confirmation of this assignment was afforded by significant peaks in the c.i. spectrum at 267 (MH^+–MeOH) and 239 (MH^+–HCOOMe). In another case, involving the abuse of barbiturates the presence of (II) was similarly established along with (I) and the recognized metabolites of quinalbarbitone.

We therefore have little doubt in proposing that 5-(3′-carboxybutyl)-5-ethylbarbituric acid (II) is a significant urinary metabolite of amylobarbitone, although final ratification of this assignment, and quantification of the metabolite, must await availability of the synthetic metabolite. Work on the synthesis of (II) has begun.

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‡ Our attention has been drawn to a report by Tang Inaba, & Kalow (1975) which indicated that *N*-hydroxyamylobarbitone is a significant (29% of dose) urinary metabolite of labelled amylobarbitone in two healthy male volunteers.

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