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METABOLIC HYDROXYLATION OF AMOBARBITAL ETHYL SIDE CHAIN

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Hepatic hydroxylation of amobarbital, 1, is known to yield mainly 5-(3-hydroxy-3-methyl) butyl-5-ethyl barbituric acid, 2, (γ-hydroxyamobarbital), by introduction of OH in the γ-position in the isoamyl side chain (1-4).

Another route of metabolism could consist in ethyl side chain β-oxidation. Barbital, which is more hydrophilic (log P octanol/water = 0.65) (5), yields about 2% of β-hydroxybarbital. The increase of lipophilic character (log P octanol/water = 2.07) (5) caused by the replacement of one of ethyl groups by a 3-methylbutyl chain, could allow a better β-oxidation rate for amobarbital.

In order to investigate this hypothesis, the following experiments were performed.

MATERIALS AND METHODS

Synthesis of models and study of their chemical behaviour ;

5-(2-hydroxyethyl)-5-(3-methylbutyl) barbituric acid, 3, (β-hydroxyamobarbital) and its degradation products were synthesized and characterized by thin layer and column chromatography, ^{1}H NMR and microanalysis. Their chemical behaviour, at pH 7.4 and 37°C, and their stability under extraction conditions were studied.

Oral administration of amobarbital to dogs.

	DOGS				
	Sex	Weight	Dose	Days	Total
Experiment A	♀	23 kg	20 mg/kg/day	10	4.6g
Experiment B	♀	8 kg	20 mg/kg/day	17	2.7g
Experiment C	♀	9.1 kg	22 mg/kg/day	20	4g

Table 1 : Conditions of administration

Isolation of metabolites from urines.

Urines were collected, stored (-18°C), extracted (PH 6.5) with ethyl acetate. Extracts were subjected to preparative column chromatography (support : Kieselgel 60 H ® ; pressure : 4 bar ; solvent : chloroform).

Identification of isolated compounds.

Thin layer and column chromatography, ^1H NMR and microanalysis were used.

RESULTS

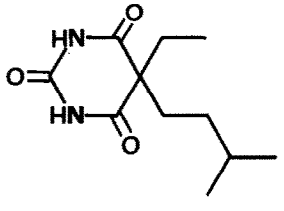
	Amobarbital 1	γ-OH Amobarbital 2	β-OH Amobarbital 3 and its degradation products
Experiment A	1	65	4.35 (β-OH 2.7)
Experiment B	1	61.3	4.44 (β-OH 2.5)
Experiment C	1	62.5	4.30 (β-OH 2.4)

Table 2 : Percentages of products extracted from urines of dogs (administered amobarbital = 100%).

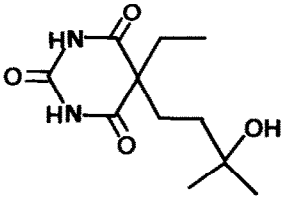
γ-Hydroxyamobarbital is the major oxidation product but 4-4.5 % of administered amobarbital are excreted as β-hydroxyamobarbital or its degradation products (corresponding allophanoyl γ-valerolactone and carboxy γ-valerolactone).

CONCLUSION

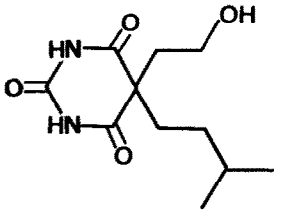
Ethyl side chain β-oxidation is one of metabolic pathways of amobarbital biotransformation. The rate of this degradation, for this lipophilic compound, is twice as high as for barbital, (Δ log P = 1.42), even if γ-hydroxylation of the other chain is here the main process.



AMOBARBITAL



γ-OH AMOBARBITAL



β-OH AMOBARBITAL

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