# METABOLISM OF ANTICONVULSANT DRUGS

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## INTRODUCTION

A considerable number of drugs have anti-epileptic properties. A relatively small number of these drugs have their anti-convulsant properties sufficiently divorced from their sedative ones, and possess adequate long-term safety, for them to be used in man to protect against epilepsy. The present review deals only with those anticonvulsant drugs that are well established as satisfactory treatments for human epilepsy. Such anticonvulsants include members of the following chemical families:

1. hydantoins – phenytoin (diphenylhydantoin), methoin, ethotoin
2. barbiturates and desoxybarbiturates – phenobarbitone, N-methylphenobarbitone, primidone (desoxyphenobarbitone)
3. dibenzodiazepines – carbamazepine
4. succinimides – ethosuximide, phensuximide, methsuximide
5. oxazolidinediones – troxidone
6. benzodiazepines – clonazepam, nitrazepam
7. valproic acid and its salts
8. butanesulthams – sulthiame.

With the exception of primidone, and probably sulthiame (about which relatively little is known), these anticonvulsants are cleared from the human body chiefly by biotransformation. The pathways of metabolism of the various drugs are known with different degrees of completeness, but information on quantitative aspects of their biotransformations is often scanty.

In the review that follows, qualitative aspects of anticonvulsant metabolism are discussed first, and then quantitative aspects, in relation to the individual anticonvulsant agents.

## HYDANTOINS

Phenytoin (diphenylhydantoin) is the main hydantoin derivative in current use. A moderate amount of information is available on its patterns of biotransformation. Methoin ("Mesantoin") is now little used because of its occasional, but very serious, bone marrow toxicity. Something is known of its metabolism. Ethotoin is a relatively ineffective drug, is little used and has been the subject of little metabolic study.

### *Phenytoin*

*Qualitative Aspects*

In man, the main metabolic pathway for phenytoin (5,5'-diphenylhydantoin) involves oxidation at the p-position on one of the phenyl rings attached to the C 5 position of the hydantoin ring /1,2/. The resulting phenolic metabolite 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-hydroxyphenytoin, HPPH) may be conjugated with glucuronic acid before excretion in urine as p-hydroxyphenytoin glucuronide (Fig. 1). p-hydroxyphenytoin is thought to be pharmacologically inactive (Butler /1/). Such oxidation, occurring in liver microsomes and catalysed by the non-specific microsomal mixed oxidase system /3/, may yield other phenolic type derivatives. There have also been reports of the formation of metabolites of phenytoin resulting from hydantoin ring scission, and from N-glucuronide formation.

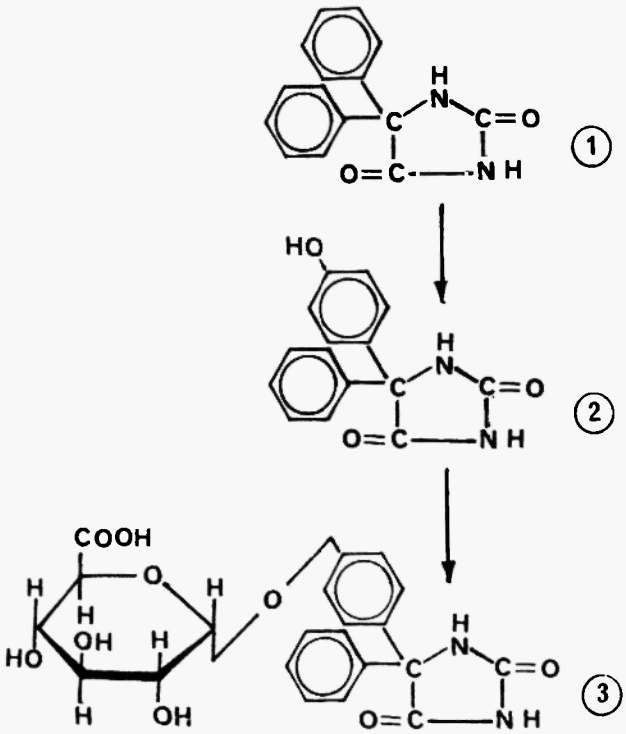



**Fig. 1.** Major pathway of phenytoin metabolism
1) phenytoin 2) 5-(p-hydroxyphenyl)-5-phenylhydantoin
3) phenytoin-O-glucuronide.

Apart from p-hydroxy phenytoin(2), reported benzene ring oxidation products of phenytoin include the following (numbered to correspond with Fig. 2):

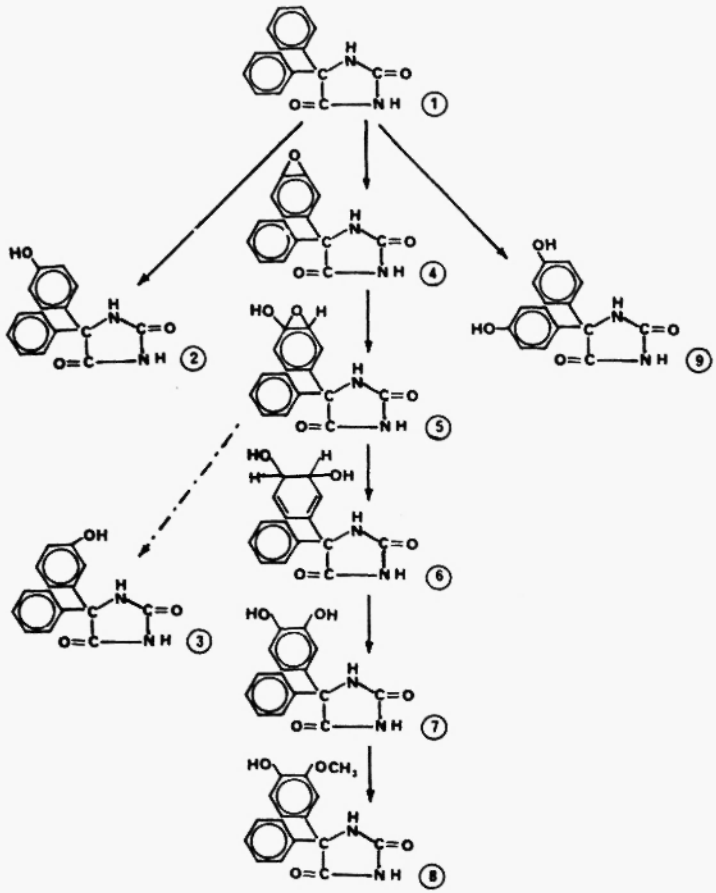


**Fig. 2.** Benzene ring oxidation products of phenytoin metabolism
1) phenytoin 2) p-hydroxyphenytoin 3) m-hydroxyphenytoin 4) epoxide metabolite 5) epoxide-ol metabolite 6) dihydrodiol metabolite 7) catechol metabolite 8) methylcatechol metabolite 9) bis-p-hydroxyphenyl metabolite.

(3) 5-(m-hydroxyphenyl)-5-phenylhydantoin, the m-isomer of p-hydroxy phenytoin. This m-isomer has been reported present in human urine on several occasions /4-6/. However, it seems likely that it is not a natural phenytoin metabolite, but is an artefact produced from a dihydrodiol metabolite of the drug (6) below, during acid hydrolysis of urine which has been carried out to separate primary metabolites from their glucuronide conjugates.

(5) an epoxide-ol metabolite, reportedly found in rat urine /7/.

(6) 5-(3,4-dihydroxy-1,5-cyclohexadine-1-yl)-5-phenylhydantoin, a dihydrodiol metabolite which appears to form in man /4, 8-10/.

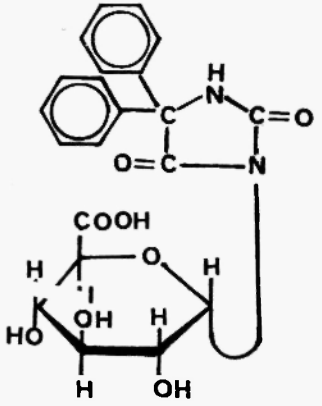
(7) 5-(3,4-dihydroxyphenyl)-5-phenylhydantoin, a catechol type derivative, found in both rat /11-14/ and human urine /15/. It is thought to be derived from the dihydrodiol metabolite /6/.

(8) 5-(4-hydroxy-3-methoxyphenyl)-5-phenylhydantoin), a methyl derivative of (7), has been found in the urine of rats /14, 16/ and of humans /15/.

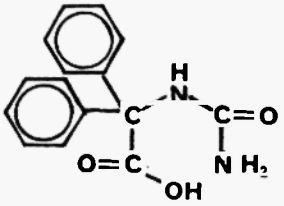
(9) 5-5-bis(4-hydroxyphenyl) hydantoin, a p-hydroxy derivative of both phenyl rings of the molecule. This is a minor metabolite, described in both rat /11/ and human /15/ urine.

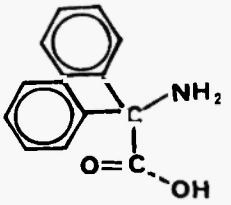
It has been suggested that initially one benzene ring on the phenytoin molecule may be oxidised to an unstable epoxide derivative which then proceeds to form the dihydrodiol /6/ and subsequent /18/ metabolites. The postulated formation pathways of the various benzene ring oxidation products of phenytoin are set out in Fig. 2. Many of these derivatives appear to form O-glucuronide derivatives before excretion in urine.

Phenytoin has also been described, in both rats and humans, as forming an N-glucuronide conjugate /19/.



Relatively early work identified two hydantoin ring scission products as metabolites of phenytoin in humans /20/. These substances, diphenylhydantoic acid and α-amino-diphenylacetic acid, do not appear to have been described subsequently in man, though the former has been found in the urine of rats given phenytoin /8/.




*Quantitative Aspects*

It is generally agreed that p-hydroxyphenytoin is the main metabolite of phenytoin. However, figures in the literature for the proportion of a phenytoin dose excreted in urine as this metabolite (together with its glucuronide conjugate) vary, e.g. 60% /21/; 75% /22/; 81% /23/; 59-88% /24/. Personal experience has been that urinary p-hydroxyphenytoin excretion may show considerable variation from day to day in the one subject. Therefore steady state urinary excretion of this metabolite needs to be followed for several consecutive days to obtain a reliable estimate of the mean daily excretion. A study in a small group of patients /25/ suggested that the proportion of the daily phenytoin dose excreted as p-hydroxyphenytoin (and its glucuronide) may decrease as plasma phenytoin concentration becomes higher, though at therapeutic concentrations the percentage excreted as the metabolite remained above 50%. It is now generally accepted that phenytoin follows Michaelis-Menten kinetics more closely than linear elimination kinetics, and the study of Bochner *et al.* /26/ in a single patient showed that the saturable elimination of the drug was due to limited capacity to form p-hydroxyphenytoin.

In human plasma, as in urine, the great majority of the p-hydroxyphenytoin is present as the glucuronide conjugate. Plasma levels of the unconjugated metabolite are about 1% /27/, or less than 6% /28/ of the total plasma levels of the metabolite. Probably about 45% of the conjugate in plasma is bound to plasma proteins /29/, though the unconjugated metabolite may be more highly bound /30/. The metabolite and its

conjugate appear to form rapidly. Within 30 to 60 minutes of a patient's first ever dose of phenytoin, measurable p-hydroxyphenytoin is present in his plasma /31/.

Steady-state plasma phenytoin levels, relative to dose, may change in certain physiological circumstances, e.g. pregnancy /32/ and in response to a number of drug-drug interactions /31/. No convincing evidence has yet been presented that these altered relationships between drug dose and drug plasma level are due to altered rates of p-hydroxyphenytoin formation, though it is possible that urinary p-hydroxyphenytoin excretion has not been followed for a long enough period to allow a clear picture to emerge.

No detailed quantitative work appears to have been done on other phenytoin metabolites.

## METHOIN

### *Qualitative Aspects*

Methoin (5-ethyl-5-phenyl-3-methylhydantoin) is N-demethylated in the animal body to form 5-ethyl-5-phenylhydantoin ('Nirvanol') /33/. Nirvanol is an anticonvulsant, but may cause aplastic anaemia. The phenyl ring on this compound is subsequently oxidised to a p-hydroxyphenyl derivative which is excreted in urine as its glucuronide conjugate /34/ – Fig. 3.

### *Qualitative Aspects*

In patients treated with methoin, plasma levels of the N-dealkylated metabolite 'Nirvanol' come to be some 10 or more times greater than plasma levels of the parent substance /35/. The metabolite is more slowly cleared than the parent substance. As yet there are no good data on the proportion of a methoin dose accounted for by its known metabolites. Since the drug is disappearing from use because of its toxicity, it seems unlikely that this information will become available.

## ETHOTOIN

### *Quantitative Aspects*

The pattern of metabolism of ethotoin (5-phenyl-3-ethylhydantoin) in dogs is similar to that of methoin. There is N-dealkylation (at the 3

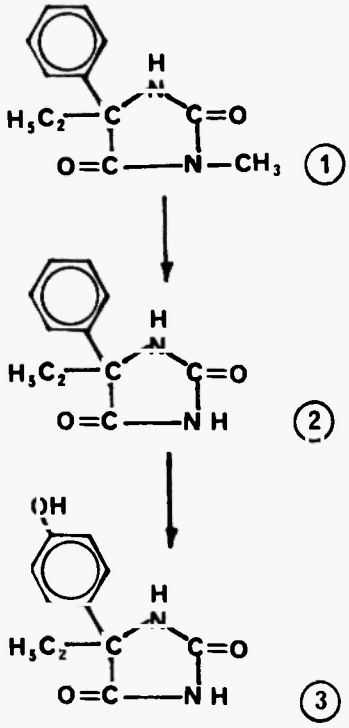
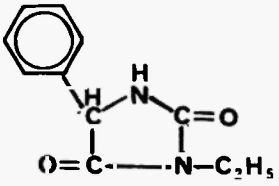


Fig. 3. Methoin metabolism
1) methoin 2) N-desmethyl metabolite ('Nirvanol')
3) p-hydroxyphenyl-N-desmethyl derivative

position), and aromatic ring hydroxylation, followed by glucuronic acid conjugation /36/.



*Quantitative Aspects*

In man ethotoin is cleared mostly by metabolism. There is some tentative evidence that the metabolism may be capacity-limited at therapeutic drug dosage /37/.

## BARBITURATES AND DESOXYBARBITURATES

Methylphenobarbitone and primidone (desoxyphenobarbitone) to a significant extent in man serve as prodrugs for phenobarbitone. It is therefore convenient to deal with the metabolism of phenobarbitone before that of its congeners.

### PHENOBARBITONE

#### *Qualitative Aspects*

The pattern of phenobarbitone metabolism is in many ways analogous to the pattern of phenytoin metabolism. The main group of known metabolites is formed by oxidation of the phenyl ring. The alkyl side-chain on the molecule may also undergo oxidation, there may be barbiturate ring opening and rearrangement, and an N-conjugation to the heterocyclic ring has been described, though the conjugating material is glucose, rather than glucuronic acid. The structures of the known phenolic type metabolites of phenobarbitone are shown in the left side of Fig. 4, with the structures of the other three known metabolites set out in the right side of this Figure.

Till recently, p-hydroxyphenobarbitone was considered to be the main metabolite of phenobarbitone. It was described as long ago as 1956 /38/. It is present in urine mainly as its glucuronide conjugate. In 1977 Tang, Inaba and Kalow /39/ described another major metabolite of phenobarbitone which they then identified as the N-hydroxide. Subsequently they revised the identification and showed that this metabolite was in fact the N-glucoside /40/. The dihydrodiol metabolite was described by Harvey *et al.* /41/, the catechol by Horning *et al.* /42/, the hydroxyethyl by Glazko /43/ and the α-phenyl-γ-butyrolactone by Andresen *et al.* /44/.

#### *Quantitative Aspects*

Figures in the literature for the proportion of a phenobarbitone dose excreted unchanged in urine have varied from 10-30% /45/ to 67% /46/. Probably the most reliable estimation is that of Whyte and Dekaban /47/ – 25%. The later authors found that an average of 17% of the dose could be accounted for as p-hydroxyphenobarbitone, while the work of Tang *et al.* /40/ in different patients suggested that some 30% of a phenobarbitone dose was excreted as the N-glucoside. Hence about 25% of the dose appears to remain unaccounted for. The quantitative con-

**Fig. 4.** Pathways of phenobarbitone metabolism

1) phenobarbitone (5-phenyl-5-ethyl barbituric acid) 2) p-hydroxyphenobarbitone (5-(p-hydroxyphenyl)-5-ethyl barbituric acid) 3) dihydrodiol metabolite (5-(3,4-dihydroxy-1,5-cyclohexadiene-1-yl)-5 ethyl barbituric acid) 4) catechol metabolite (5-(3,4-dihydroxypheny)-5-ethyl barbituric acid) 5) hydroxyethyl metabolite (5-phenyl-5-hydroxyethyl barbituric acid) 6) phenobarbitone-N-glucoside 7) α-phenyl-γ-butyrolactone.

tribution of the other known (minor) metabolites of the drug to this 25% is uncertain.

There are no clear data on the effects of physiological factors, disease and other (interacting) drugs on patterns of phenobarbitone metabolism. The clearance of the parent substance may be altered by these factors /31/, but altered metabolite production has not been demonstrated.

## METHYLPHENOBARBITONE

### *Qualitative Aspects*

Methylphenobarbitone has conventionally been regarded as a poorly absorbed substance which was biotransformed to phenobarbitone and excreted as such /48/, or as p-hydroxy-phenobarbitone. Recent studies in the author's laboratory /49/ have defined p-hydroxymethylphenobarbitone as a major metabolite of methylphenobarbitone. Meta isomers of both p-hydroxyphenobarbitone and p-hydroxymethylphenobarbitone have been identified in human urine after acid hydrolysis but not after glururonidase hydrolysis. This suggests that these m-isomers may be methodological artefacts arising from extracorporeal reactions with postulated dihydrodiol metabolites of both methylphenobarbitone and phenobarbitone. Small amounts of presumptively identified O-methyl-catechol metabolites of both methylphenobarbitone and phenobarbitone have also been found by mass spectral studies on urine from patients taking methylphenobarbitone. A scheme of methylphenobarbitone metabolism is set out in Fig. 5.

### *Quantitative Aspects*

Recent work /50/ suggests that methylphenobarbitone is about 75% bioavailable. Very little unchanged drug is excreted in urine. Some 70% of the absorbed drug can be accounted for in urine as p-hydroxy-methylphenobarbitone, phenobarbitone or p-hydroxy-phenobarbitone (the phenolic derivatives being present mainly as glucuronide conjugates). The main metabolite, accounting for almost 50% of the absorbed dose, proved to be p-hydroxyphenyl methylphenobarbitone, but phenobarbitone accounted for nearly 20% of the absorbed dose /51/. No data are available on modifications of methylphenobarbitone metabolism by physiological or pathological factors, or by intake of other drugs.

**Fig. 5.** Pathways of methylphenobarbitone metabolism

1) N-methylphenobarbitone (5-ethyl-1-methyl-5-phenyl barbituric acid) 2) phenobarbitone 3) p-hydroxy derivative of methylphenobarbitone 4) dihydrodiol derivative of methyl phenobarbitone 5) p-hydroxy derivative of phenobarbitone 6) dihydrodiol derivative of phenobarbitone 7) methy catechol derivative of methylphenobarbitone 8) m-hydroxyphenyl derivative of methylphenobarbitone 9) methylcatechol derivative of phenobarbitone 10) m-hydroxyphenyl derivative of phenobarbitone.

## PRIMIDONE

### *Qualitative Aspects*

Primidone (desoxyphenobarbitone) is known to undergo *in vivo* oxidation to phenobarbitone /52/. The latter substance then presumably undergoes its usual pattern of metabolism. Primidone also undergoes ring opening, forming phenylethylmalonamide (Fig. 6). Both phenobarbitone and phenylethylmalonamide are anticonvulsants in their own right.

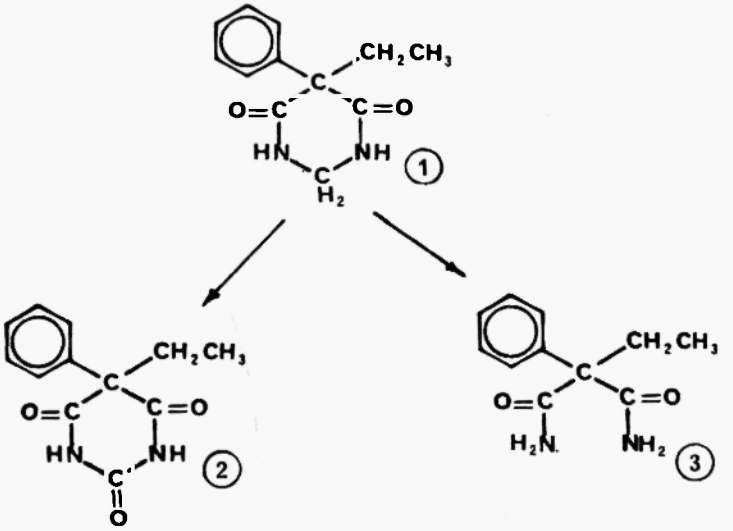



**Fig. 6.** Pathway of primidone metabolism
1) primidone (2-desoxyphenobarbitone) 2) phenobarbitone 3) phenylethylmalonamide

### *Quantitative Aspects*

There is wide variation in the amount of a primidone dose excreted unchanged in urine – 15 to 66% /53/. Only 1 - 8% of the dose is converted to phenobarbitone /53/. The portion of the dose (16 - 65%) not accounted for as parent drug or phenobarbitone is probably excreted in urine as phenylethylmalonamide. There are no data directly demonstrating altered primidone metabolism in response to physiological factors, disease or drug-drug interactions.

## DIBENZODIAZEPINES

### CARBAMAZEPINE

#### *Qualitative Aspects*

Carbamazepine is the only dibenzodiazepine derivative in current use as an anticonvulsant. The drug is believed to undergo two main pathways of metabolism. One or other of its benzene rings may be oxidised to form phenolic derivatives, or the C=C double bond in the central ring may be oxidised to form an epoxide (carbamazepine-10,11-epoxide, a proven anticonvulsant in its own right /54/).The epoxide may then yield a dihydroxy derivative which lacks anticonvulsant activity /55/. The metabolic pathways of carbamazepine (after Faigle *et al.* /56/) are shown in Fig. 7.

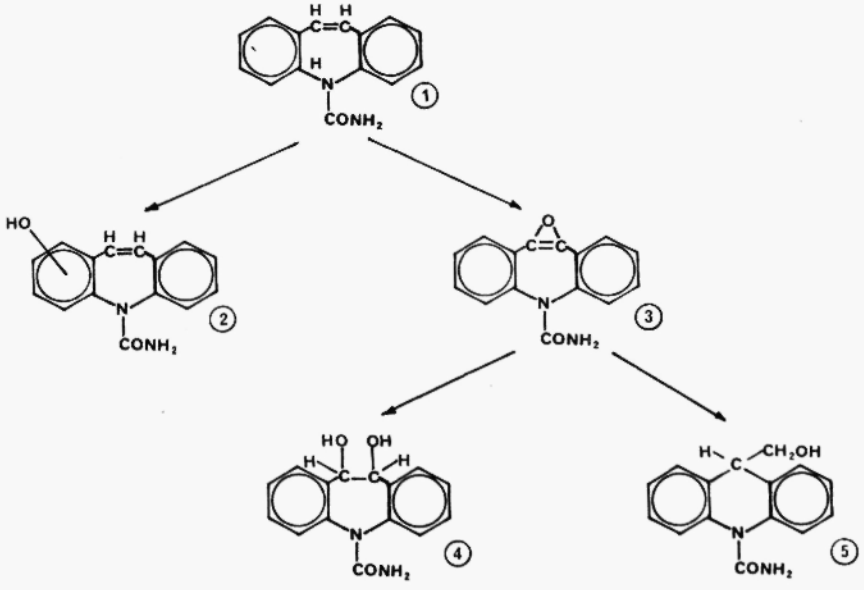



Fig. 7. Pathways of carbamazepine metabolism
1) carbamazepine (5-carbamyl-5H-dibenz[b.f]azepine) 2) phenolic derivatives 3) carbamazepine-10.11-epoxide 4) 10.11-dihydroxycarbamazepine 5) 9-hydroxymethyl-10-carbamoyl acridan.

*Quantitative Aspects*

No more than 2% of a carbamazepine dose is excreted unchanged in urine /57, 58/. Less than 2% of the dose is excreted as the epoxide /57/, but 10-30% is lost as the dihydroxy derivative. The three phenolic metabolites each account for some 2 to 10% of the dose, while the acridan derivative is excreted in trace amounts only.

Phenytoin consistently interacts with carbamazepine to cause reduced plasma carbamazepine levels /59/. Since plasma carbamazepine-10, 11-epoxide levels tend to remain unaltered in this interaction, it seems likely that carbamazepine metabolism is diverted towards metabolic pathways apart from epoxide formation /60/. However direct quantitative proof of this postulated mechanism is lacking.

## SUCCINIMIDES

Although three succinimide derivatives are in use as anticonvulsants, only ethosuximide is an important antiepileptic agent. Phensuximide and methsuximide are largely superseded drugs which are relatively ineffective.

### ETHOSUXIMIDE

*Qualitative Aspects*

In humans ethosuximide is metabolised by oxidation, forming a number of hydroxylated derivatives. The known metabolic pathways are set out in Fig. 8. The succinimide ring may itself be oxidised at the 3 position (metabolite 2) /61, 62/. The ethyl side chain at the 2 position may be oxidised to a 1 or a 2-hydroxy ethyl (metabolites 6 and 3 /61, 63/) or an acetyl derivative (metabolite 5 /61, 63/), while the second of these may be further oxidised to a carboxymethyl derivative (metabolite 4 /64/). The methyl side chain on the 2 position may be oxidised to a hydroxymethyl compound (metabolite 7 /61/). It is not known whether any of the metabolites have pharmacological activity.

*Quantitative Aspects*

Some 17 to 38% of an ethosuximide dose is excreted unchanged in human urine /43/. The main metabolite in urine is 2-(1-hydroxyethyl)-2-methylsuccinimide (its two isomers accounting for 55% of the dose /65/). The other metabolites described above collectively account for

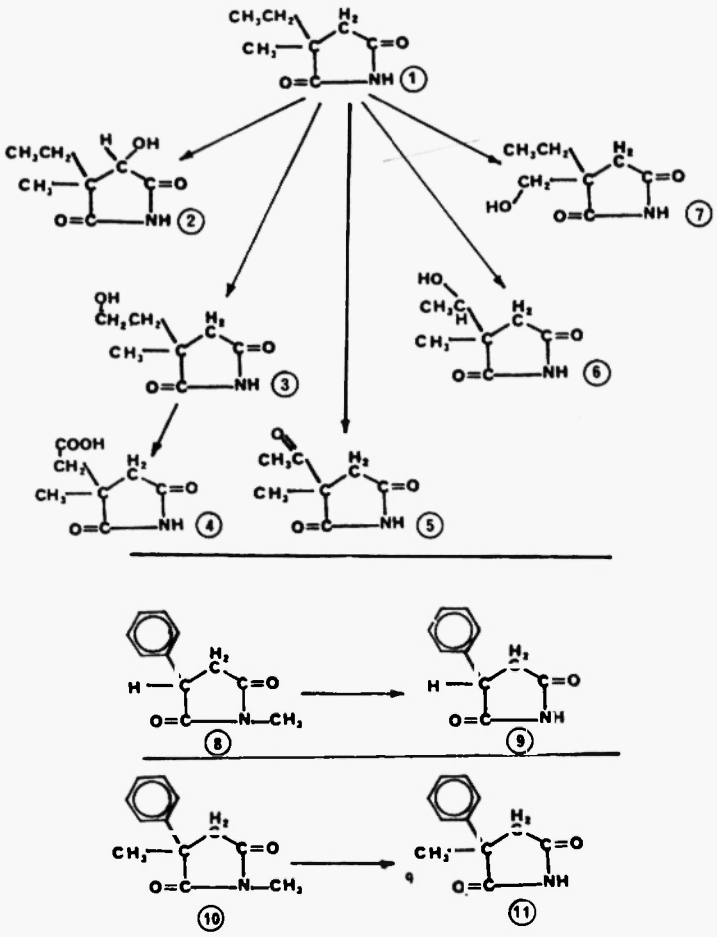


Fig. 8. Pathways of succinimide metabolism. Upper portion — ethosuximide; lower portions phensuximide and methsuximide
1) ethosuximide (2-ethyl-2-methylsuccinimide) 2) 2-ethyl-2-methyl-3-hydroxysuccinimide 3) 2-(1-hydroxyethyl)-2-methylsuccinimide 4) 2-carboxymethyl-2-methyl succinimide 5) 2-acetyl-2-methyl succinimide 6) 2-(2-hydroxyethyl)-2-methylsuccinimide 7) 2-ethyl-2-(hydroxymethyl) succinimide 8) phensuximide (N-methyl-2-phenyl-succinimide) 9) 2-phenylsuccinimide 10) methsuximide (N.2-dimethyl--2-phenylsuccinimide) 11) 2-methyl-2-phenylsuccinimide.

some 25% of an ethosuximide dose. There is no information available regarding the effects of various factors on the patterns of ethosuximide biotransformation.

### PHENSUXIMIDE

*Qualitative Aspects*

Phensuximide (Fig. 8) in man forms an N-desmethyl metabolite /66/.

### METHSUXIMIDE

*Qualitative Aspects*

Methsuximide is also N-desmethylated (Fig. 8) in both animals and man /67/. The N-desmethyl derivative appears to possess anticonvulsant activity. Because of its lower clearance it accumulates in the human body, achieving higher plasma levels than the parent substance.

## OXAZOLIDINEDIONES

..oxidone (trimethadione) is the only oxazolidinedione derivative remaining in use, but it has now become largely superseded in human therapeutics.

### TROXIDONE

In man troxidone (3,5,5-trimethyloxazolidine-2,4-dione) is said to be totally, or almost totally, N-desmethylated to dimethadione, an active anticonvulsant /68/. No other metabolic product is known, and nothing seems known of factors which may modify the human body's conversion of troxidone to its metabolite.


## BENZODIAZEPINES

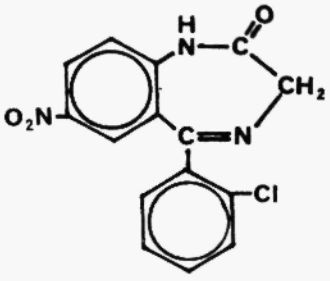
Many of the benzodiazepines have useful anticonvulsant actions, but clonazepam is the only benzodiazepine derivative marketed purely as an

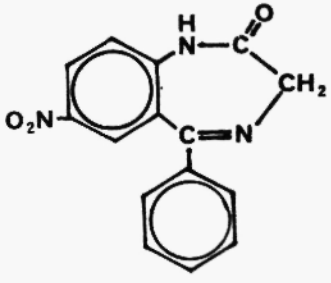
anticonvulsant. However nitrazepam at a slightly earlier time enjoyed a significant role in the long-term therapy of certain forms of epilepsy. Clonazepam and nitrazepam will be the only benzodiazepines discussed here. The drugs have very similar chemical structures and patterns of metabolism and will be considered side by side.

## CLONAZEPAM AND NITRAZEPAM

### *Qualitative Aspects*

Clonazepam (7-nitro-5-(2-chlorophenyl)-3H-1,4-benzodiazepine-2-one) and nitrazepam (7-nitro-5-phenyl-3H-1,4-benzodiazepine-2-one) have identical molecular structures except for, on clonazepam, a Cl group at the o-position on the benzene ring bonded to the 5 position of the benzodiazepine moiety.




The biotransformation pattern of clonazepam has been described by Eschenhof /69/ and that of nitrazepam by Rieder and Wendt /70/. There appear to be four main sites on these benzodiazepine molecules at which biotransformation reactions occur (Fig. 9)

(i) The $-NO_2$ group at the 7 position may be reduced, thus forming 7-amino derivatives. These are subsequently conjugated with acetate groups to form acetamide derivatives.

(ii) The C atom at the 3 position may be oxidised to a hydroxy derivative which is subsequently conjugated with glucuronic acid prior to excretion in urine.

(iii) In the case of clonazepam, either benzene ring of the 7-amino derivative may be oxidised to form a phenol, though the exact oxidation site on the molecule does not appear to have been determined.

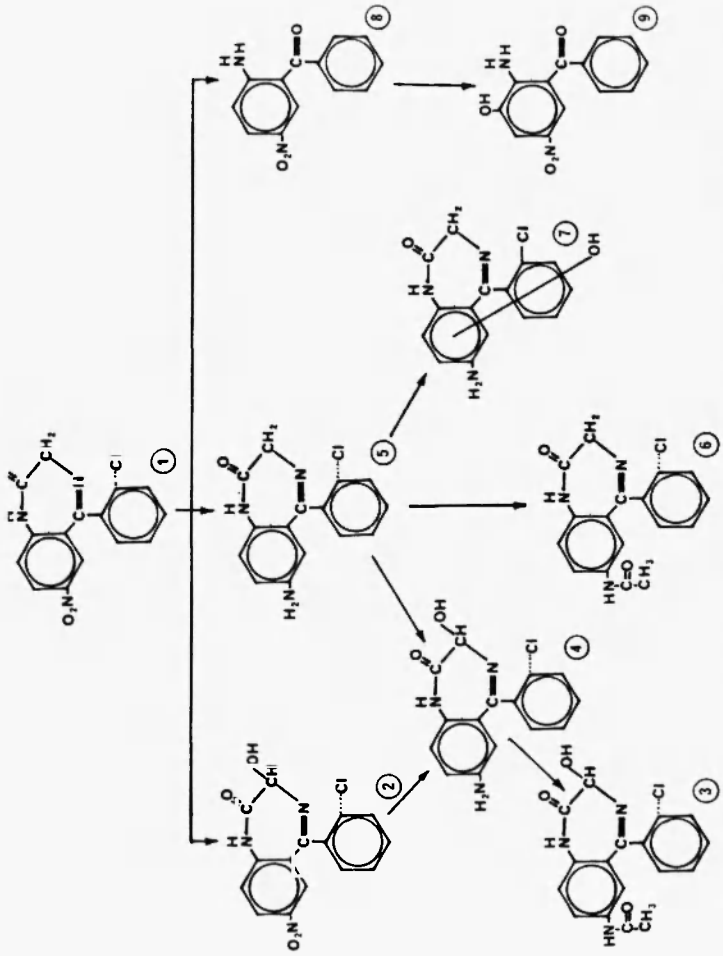


**Fig. 9.** Pathways of metabolism of 7-nitrobenzodiazepine anticonvulsants (clonazepam and nitrazepam). The bond attaching the Cl atom to the lower benzene ring is shown as a solid line when the metabolite is known for clonazepam only and as a broken line when analogous metabolites form from both benzodiazepines. No bond and no Cl atom are shown if the metabolite derives from nitrazepam only. 1) clonazepam and nitrazepam 2) 3-hydroxyderivatives 3) 3-hydroxy-7-acetamide derivatives 4) 3-hydroxy-7-amino derivatives 5) 7-amino derivatives 6) 7-acetamido derivatives 7) phenolic derivative of clonazepam 8) benzophenone and hydroxybenzophenone 9) metabolites of nitrazepam.

(iv) In the case of nitrazepam, diazepine ring scission may occur, forming a benzophenone derivative. The benzene ring of this derivative may then be oxidised to form a phenolic compound.

In second stage biotransformations, the 7-amino metabolites may undergo hydroxylation at the -3 position and the 3-hydroxy metabolites may undergo reduction of the nitro group at the 7 position. The 7-amino-3-hydroxy derivatives thus formed may subsequently undergo acetate conjugation at the 7-amino groups, forming 7-acetamide derivatives.

*Quantitative Aspects*

Little useful information is available regarding quantitative aspects of clonazepam and nitrazepam metabolism. Figures for the percentage of a clonazepam dose excreted unchanged in human urine are 2% /71/, 0.1-1.4% /72/ and 0.2% /73/. The 7-amino derivative of both clonazepam and nitrazepam are the main metabolites found in human plasma, but this does not necessarily mean that they are the major metabolites of the drugs in urine. The amino derivatives may simply be cleared more slowly than quantitatively more important metabolites.

## VALPROIC ACID

Valproic acid, often administered as its sodium salt, differs in chemical structure from the other anticonvulsants in common use. Rather than being a small heterocyclic molecule it is a short branched-chain fatty acid (n-propyl pentanoic acid; di-n-propylacetic acid).

*Qualitative Aspects*

The great majority of a valproate dose in man is cleared by biotransformation. A number of metabolites have been identified /74-79/. A scheme of some presumptive metabolic pathways is shown in Fig. 10. The valproic acid molecule appears to undergo either beta or omega oxidation, but also direct conjugation with glucuronic acid. Products of beta-oxidation may ultimately enter the Krebs cycle and in rats 15-20% of a valproate dose is excreted as expired $CO_2$. Other as ye identified conjugates of the drug appear to exist in human and an urine /80, 81/. In rats the glucuronide conjugate appears to undergo entero-hepatic circulation /81/.

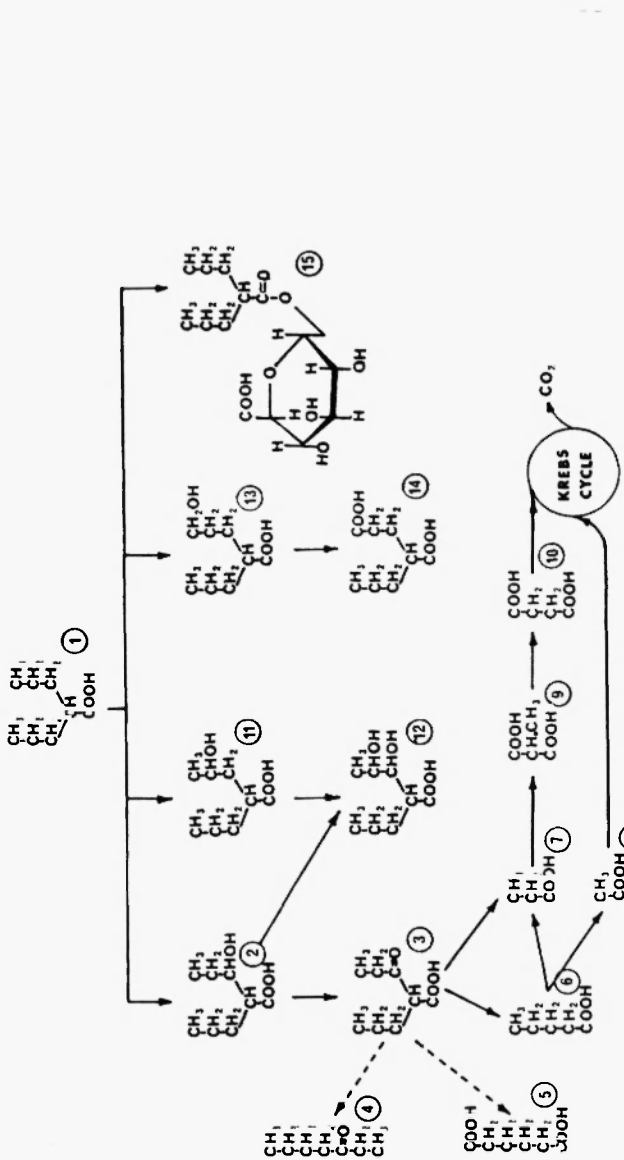



**Fig. 10.** Pathways of valproic acid metabolism
1) valproic acid (n-propyl-pentanoic acid) 2) 3-hydroxy-2-n-propylpentanoic acid 3) 3-oxo-2-n-propylpentanoic acid 4) 3-heptanone 5) glutaric acid 6) pentanoic (valeric) acid 7) propionic acid 8) acetic acid 9) malonic acid 10) succinic acid 11) 4-hydroxy 2 n-propyl-pentanoic acid 12) 3 4-dihydroxy 2 n propylpentanoic acid 13) 5-hydroxy 2 n-propylpentanoic acid 14) 2-n-propyl glutaric acid 15) 2-n propyl pentanoyl glucuronide

*Quantitative Aspects*

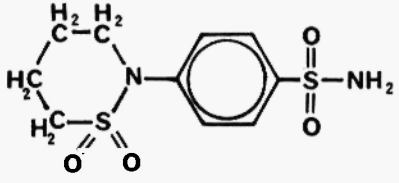
Figures for percentage of a valproate dose excreted unchanged in urine are 0% /82/, less than 1% /80/, 3.2% /83/, and 7% /84/. Some 21% of a dose is excreted as conjugated metabolites /83/. Relatively little information is available regarding the detailed quantitative composition of the valproate metabolite pattern excreted in human urine. A substantial portion of any given valproate dose still remains unaccounted for. In rats, the pattern of valproate metabolite excretion in urine appears to be dose dependent /81/. Some 4-6% of the dose is excreted as unchanged drug, and 24% and 53% as its glucuronide (at doses of 15 and 150 mg/kg) respectively. The other quantitatively significant metabolite in rat urine was n-propylglutaric acid.

In view of the relative lack of knowledge of quantitative aspects of valproate metabolism in man, there is no adequate basis for assessing possible alterations of valproate biotransformation in physiological or pathological circumstances, or in drug-drug interactions.

## BUTANESULTHAMS

### SULTHIAME

Little information is available about the metabolism of sulthiame, a substance which appears to be passing from favour as an independent antiepileptic agent. Old work /85/ indicated that 60-70% of a dose in man was excreted unmetabolised in urine. The remainder was excreted as a hydroxylated metabolite (structure unstated), devoid of pharmacological activity /86/.



## CONCLUSION

Although a moderate amount of information is available about the patterns of metabolism of the various anticonvulsant agents, it seems likely that at least some of these drugs have as yet undiscovered meta-

bolites. Knowledge of quantitative aspects of anticonvulsant metabolism in man is far from complete, partly because of the practical difficulties in carrying out the input-output metabolic balance studies necessary to generate the appropriate information. Numerous interactions between the anticonvulsants and other drugs are known, and pharmacokinetic data suggest that at least some of these interactions involve altered anticonvulsant metabolism. However, there is virtually no good quantitative metabolic data available to clarify this matter. Further, quantitative aspects of the metabolism of homologous series of anticonvulsants, e.g. the barbiturates and the benzodiazepines, in man and various animal species, remain largely unexplored. Anticonvulsant biotransformation is an area in which much further work could be done, with profit.

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