

BIOTRANSFORMATIONS

Volume 1

*A survey of
the biotransformations
of drugs and chemicals
in animals*

Edited by D. R. Hawkins

Biotransformations

*A survey of the biotransformations
of drugs and chemicals in animals*

Volume 2

Edited by

D. R. Hawkins

Huntingdon Research Centre Ltd



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Preface

The format of this second volume is identical to the first and it is hoped that this series will become increasingly useful with the publication of this and subsequent volumes.

The techniques for studying metabolism are now well established but increasing efforts are needed to ensure expeditious utilization of the knowledge that can be obtained. At no time should metabolism and toxicity studies be carried out in isolation since the two are often inextricably linked in a cause and effect relationship. The limitations of laboratory animal models for toxicological evaluation are well recognized. Comparative metabolism studies in man and laboratory animals can assist in the design of the most appropriate toxicity studies and in the interpretation of their results. The contribution of metabolism to the pharmacological profile of a drug is well accepted. Opportunities exist to utilize a knowledge of metabolism in the drug discovery process by ensuring that the intrinsic activity of new structures can be incorporated into drugs which show the desired pharmacological activity *in vivo* and which do not produce toxicological side-effects. An appropriate pharmacokinetic profile is an essential property of a successful drug and in many cases this is determined by the types of biotransformation processes which occur and the rates of these processes.

This series encompasses biotransformations of chemical entities whether they are pharmaceuticals, agrochemicals, food additives, or environmental or industrial chemicals in vertebrates within the animal kingdom, a group which includes mammals, birds, fish, amphibians, and reptiles. Each volume of the series will in general include material published during a calendar year, this second volume covering 1988. An attempt has been made to include a comprehensive coverage of the scientific literature but due to the great diversity of journals where reports on biotransformations appear, there will undoubtedly be some omissions. Any notable omissions communicated to the Editor could be included in a subsequent volume.

Arrangement of Material and Access

An overview chapter has been prepared which contains highlights such as novel biotransformation, mechanisms of toxicity, and notable species differences. The abstracts are arranged according to compound class, although there may be cases where allocation to one or another class is somewhat subjective. It has been considered valuable to be able to access information on the biotransformation of compounds with similar structural features. For this purpose the concept of key functional groups has been developed. Selection and naming of these groups has evolved during preparation of the material. For each compound functional groups have been selected where

biotransformation has been shown to occur but in addition groups have also been included where biotransformation has not taken place. The same functional groups may not necessarily be included in all abstracts of the same compound since some papers may be confined to specific aspects of biotransformation and here only the relevant groups are included. A list of the functional groups follows which may be referred to before proceeding to the corresponding index. Two other indexes have been included containing compound names and types of biotransformation processes respectively.

In the precis for each compound certain key information has been included when available. Where radiolabelled compounds have been used the position(s) of labelling have been indicated on the structure. Comments on the source of metabolites and information on the quantitative importance of individual metabolites such as percentage material in the sample or percentage administered dose are given where possible. Also, in order to provide a perspective on the criteria for identification, the procedures used for separation and isolation of metabolites and structural assignments such as chromatographic and physico-chemical techniques and use of reference compounds have been discussed.

The Editor

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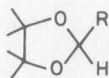
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Key Functional Groups

R may be any unspecified group including H. Where two or more R groups are indicated these may be the same or different groups. Where aromatic rings or other cyclic systems are shown they may also contain substituents when they are not specified as part of the key functional group.

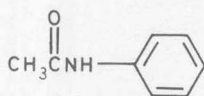
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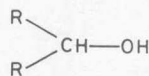
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N-Acetyl aryl amine



sec-Alkyl alcohol



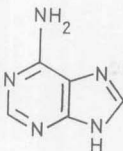
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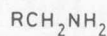
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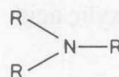
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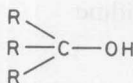
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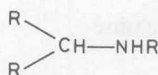
Alkyl tert-amine



tert-Alcohol



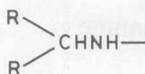
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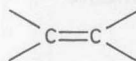
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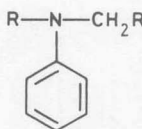
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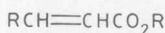
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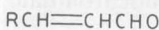
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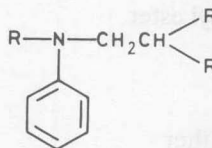
Alkene carboxylate



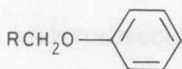
Alkenyl aldehyde

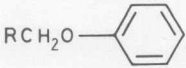
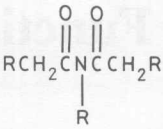
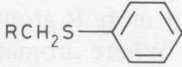

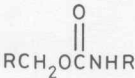

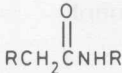
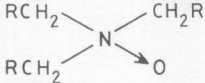
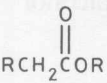
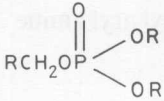

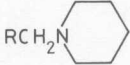
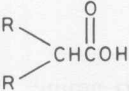
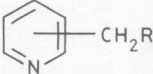
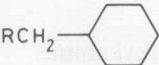
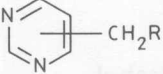
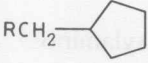


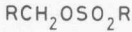
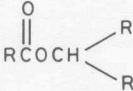
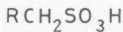

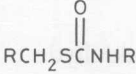
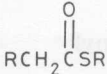


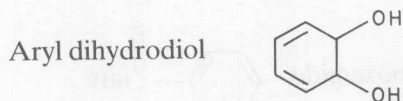
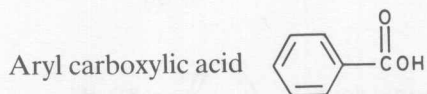
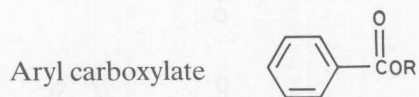
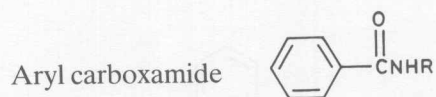
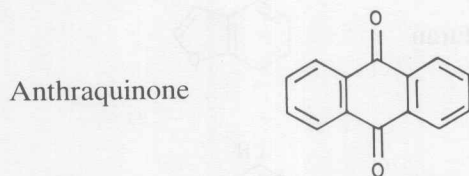
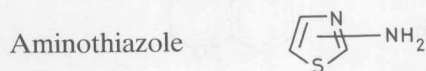
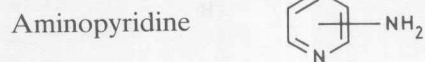
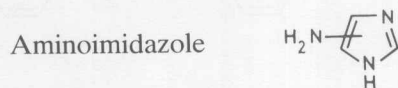
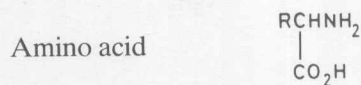
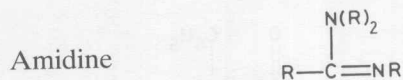
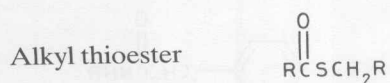
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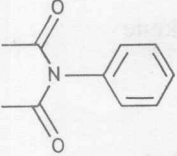
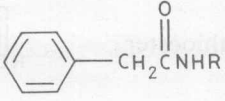
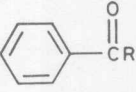
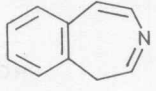
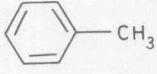
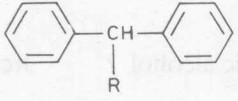
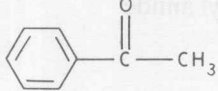
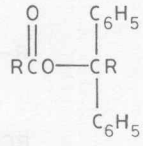
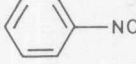
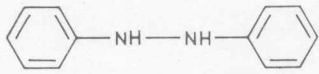
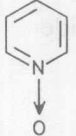
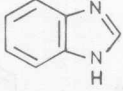
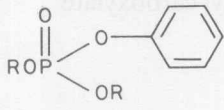
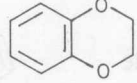
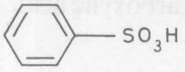
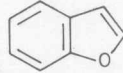
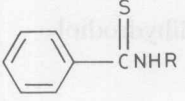
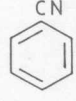
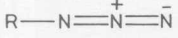
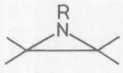
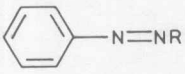
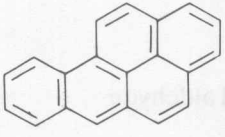


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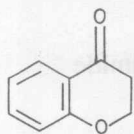


Alkyl aryl ether		Alkyl imide	
Alkyl aryl thioether		Alkyl ketone	
Alkyl carbamate		Alkyl nitrile	
Alkyl carboxamide		Alkyl N-oxide	
Alkyl carboxylate		Alkyl phosphate	
Alkyl carboxylic acid		N-Alkylpiperidine	
iso-Alkyl carboxylic acid		Alkylpyridine	
Alkylcyclohexane		Alkylpyrimidine	
Alkylcyclopentane		Alkyl sulphamate	
Alkyl ester		Alkyl sulphonate	
iso-Alkyl ester		Alkyl sulphonic acid	
Alkyl ether		S-Alkyl thiocarbamate	
		Alkyl thiocarboxylate	

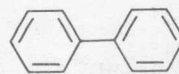


N-Arylimide		Benzamide	
Aryl ketone		Benzazepine	
Arylmethyl		Benzhydryl	
Aryl methyl ketone		Benzhydryl ester	
Arylnitroso		Benzidine	
Aryl N-oxide		Benzimidazole	
Aryl phosphate		Benzodioxin	
Aryl sulphonic acid		Benzofuran	
Aryl thiocarboxamide		Benzonitrile	
Azide			
Aziridine			
Azobenzene		Benzo[a]pyrene	

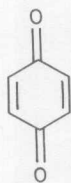
Benzopyranone



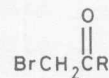
Biphenyl



Benzoquinone



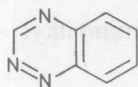
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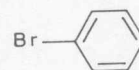
Bromoalkane



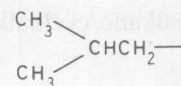
Benzotriazine



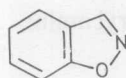
Bromophenyl



iso-Butyl



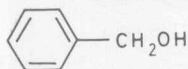
Benzoxazole



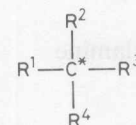
Carbamate



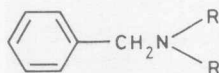
Benzyl alcohol



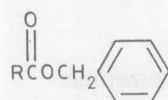
Chiral carbon



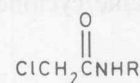
Benzyl amine



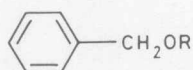
Benzyl ester



Chloroacetamide



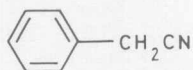
Benzyl ether



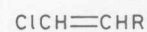
Chloroalkane



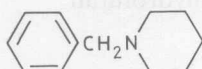
Benzyl nitrile



Chloroalkene



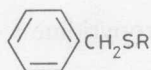
N-Benzylpiperidine



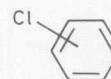
Chloroalkyl



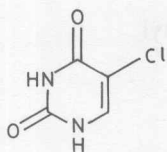
Benzyl thioether



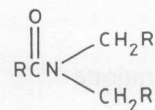
Chlorophenyl



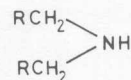
Chlorouracil



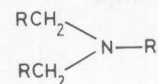
Dialkyl amide



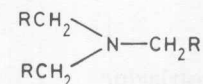
Dialkyl amine



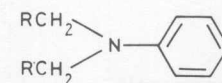
Dialkylamino



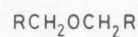
Dialkylaminoalkyl



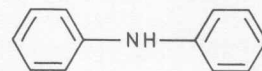
Dialkyl aryl amine



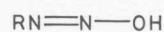
Dialkyl ether



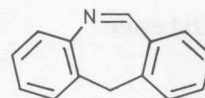
Diaryl amine



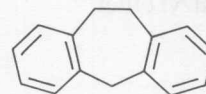
Diazohydroxide



Dibenzazepine



Dibenzocycloheptane



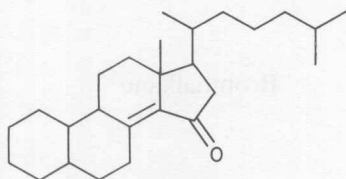
Dihydrofuran



Dihydropyridine



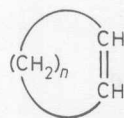
Cholestenone



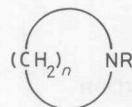
Cycloalkane/cycloalkyl



Cycloalkene



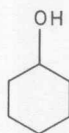
Cycloalkylamine



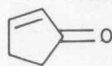
Cyclohexane/cyclohexyl



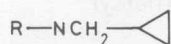
Cyclohexanol



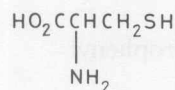
Cyclopentenone

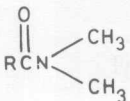
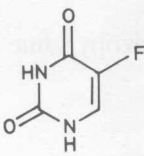
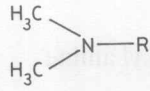
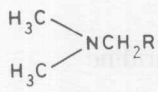

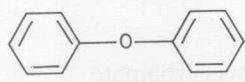

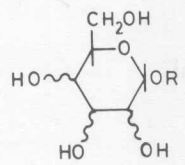

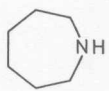
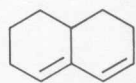
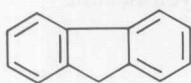
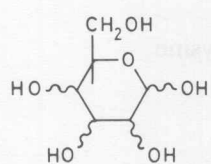
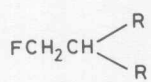
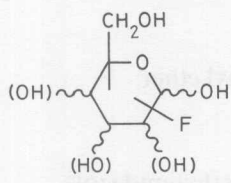
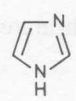
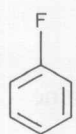



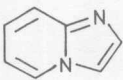
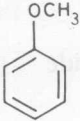
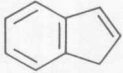
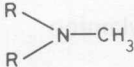
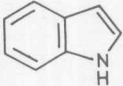
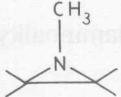

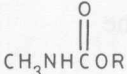
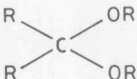

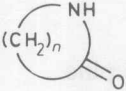
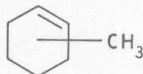
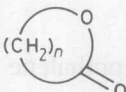
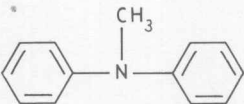
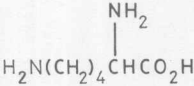

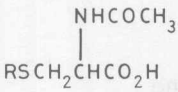
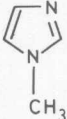
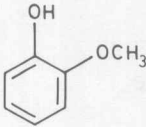

N-Cyclopropylmethyl

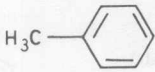
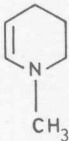

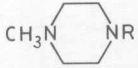
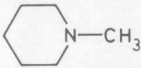
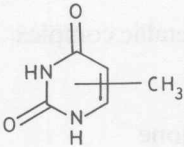
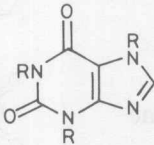

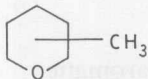
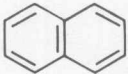
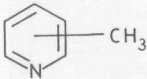
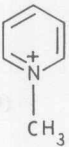
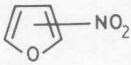

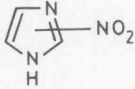

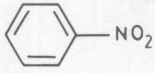
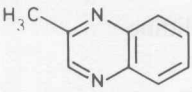
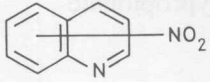
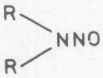


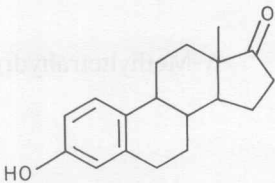
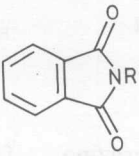
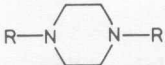
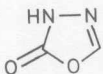



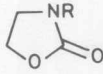

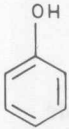
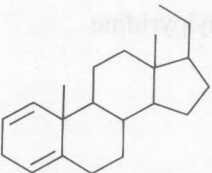
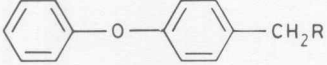
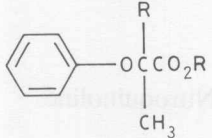
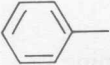
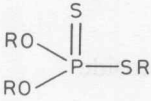



Cysteine

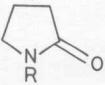
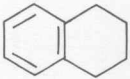
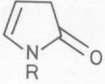

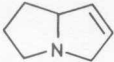

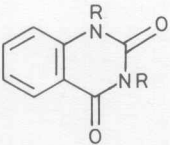
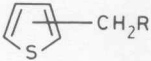
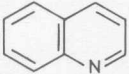
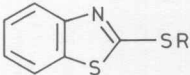
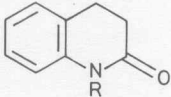

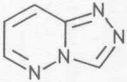
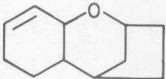
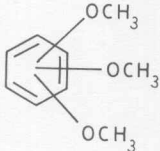
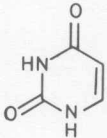
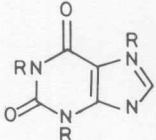
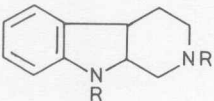


Dimethylamide		Fluorouracil	
Dimethylamino		Formamide	RNHCHO
Dimethylaminoalkyl		Furan	
Diphenyl ether		Glutathione	$\text{HOOCCH(NH}_2\text{)CH}_2\text{CH}_2\text{CO-NHCH(CH}_2\text{SH)CO-NHCH}_2\text{COOH}$
Dioxolane		Glycoside	
Epoxide		Hexahydroazepine	
Fatty acid	$\text{R(CH}_2\text{)}_n\text{CO}_2\text{H}$	Hexahydronaphthalene	
Fluorene		Hexose	
Fluoroalkyl		Hydrazone	RCH=NNHR
Fluorohexose		Imidazole	
Fluorophenyl		Imidazoline	

Imidazopyridine		Methoxyphenyl	
Indene		<i>N</i> -Methyl alkyl amine	
Indole		<i>N</i> -Methylaziridine	
Iodoalkyl	ICH_2R	Methyl carbamate	
Isothiocyanate	$\text{RN}=\text{C}=\text{S}$	<i>N</i> -Methylcarbamate	
Ketal		Methyl carboxylate	
Lactam		Methylcyclohexene	
Lactone		<i>N</i> -Methyl diaryl amine	
Lysine		Methyl ester	
Mercapturic acid		Methyl ether	CH_3OR
Methanesulphonate	$\text{CH}_3\text{SO}_2\text{OR}$	<i>N</i> -Methylimidazole	
<i>o</i> -Methoxyphenol		<i>N</i> -Methylnitrosamine	

Methylphenyl		<i>N</i> -Methyltetrahydropyridine	 
<i>N</i> -Methylpiperazine			
<i>N</i> -Methylpiperidine		Methyluracil	
<i>N</i> -Methylpurine	 R = H or CH ₃	Morpholine	
Methylpyran		Naphthalene	
Methylpyridine		Nitrile	RCN
<i>N</i> -Methylpyridinium		Nitrofur	
<i>N</i> -Methylpyrrolidine		Nitroimidazole	
<i>N</i> -Methylpyrrole		Nitrophenyl	
Methylquinoxaline		Nitroquinoline	
		Nitrosamine	
		Nucleoside	—

Oestrone		Phthalimide	
Organometallic complex	—	Piperazine	
Oxadiazolone		Piperidine	
Oxazole		Piperidinedione	
Oxazolidinone		Platinum	—
Peptide		Polycyclic aromatic hydrocarbon	—
Phenol		Pregnadiene	
Phenoxybenzyl		N-Propyl	$(R)_2NCH_2CH_2CH_3$
Phenoxypropionate		Propynyl	$CH_3C\equiv C-$
Phenyl		Prostanoid	—
Phosphorodithioate		Pyrazine	
		Pyridine	
		Pyrrolidine	

Pyrrolidinone		Tetrahydronaphthalene	
Pyrrolidone		Thiazole	
Pyrrolizidine		Thiazolidine	
Quinazolidinedione		Thienylalkyl	
Quinoline		Thiobenzothiazole	
Quinolinone		Triazine	
Steroid	—	Triazolopyridazine	
Sterol	—	Trichothecene	
Sulphenamide	$R-S-N(R)_2$	Trimethoxyphenyl	
Sulphonamide	RSO_2NHR	Uracil	
Sulphonylurea	$RSO_2NHC(=O)NHR$	Xanthine	
Terpene	—		
Tetrahydrocarboline			
Tetrahydroisoquinoline	