BIOTRANSFORMATIONS

Volume 2

A survey of the biotransformations of drugs and chemicals in animals

Edited by D. R. Hawkins

Biotransformations

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Volume 1

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D. R. Hawkins

Huntingdon Research Centre Ltd

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Preface

Investigation of biotransformation processes has been a rapidly expanding aspect of xenobiotic metabolism. This has been brought about by the increasing realization of the important influence of biotransformation on pharmacological activity and toxicity and the parallel rapid advances in technology in analytical chemistry and in particular physico-chemical techniques such as mass spectrometry.

In drug discovery and development extrapolation of activity from *in vitro* pharmacological screens to animals *in vivo* and finally to man can be improved by consideration of the impact of biotransformation on the compound in different systems. Consideration of the structures of compounds shown to be active in *in vitro* screens would indicate compounds likely to be inactive *in vivo* due to rapid biotransformation. Structural modifications can then be introduced to inhibit metabolism at key positions in the molecule.

Species differences in toxicity are commonplace and are often attributable to differences in biotransformation pathways. An understanding of the mechanisms of toxicity may help to extrapolate the relevance of findings in laboratory animals to human exposure.

Prediction of biotransformation pathways would be an ideal goal but one which we are far from achieving. However, a key to knowing how close we can get to this goal is to ensure that full use can be made of available knowledge. This series has been devised to bring together all current information on biotransformations in a readily accessible form. It is hoped that this will provide a valuable database which will increase awareness of patterns in species differences and influences of chemical structure on biotransformation with a view to increasing the ability to make predictions for new compounds.

The series will cover biotransformations of chemical entities whether they are pharmaceuticals, agrochemicals, food additives, or environmental or industrial chemicals in vertebrates of the animal kingdom, which includes mammals, birds, fish, amphibians, and reptiles. This first volume broadly covers the literature for the calendar year 1987 although it has not been possible to include material in late issues of some journals. This will be included in the second volume which will cover 1988 literature. We have attempted to include all relevant literature but realize that this goal may not have been achieved. The Editor would be grateful to receive copies of omitted papers which 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. A list of the functional groups is provided 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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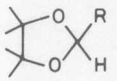
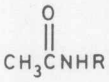
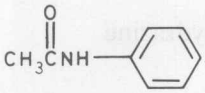
Key Functional Groups

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.

Acetal 

Acetamide 

N-Acetyl aryl amine 

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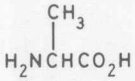
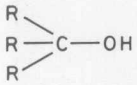
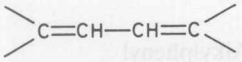
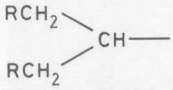
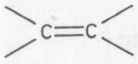
Alanine 

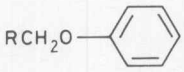
tert-Alcohol 

Alkadiene 

Alkane $CH_3(CH_2)_nR$

iso-Alkane 

Alkene 

Alkoxyphenyl 

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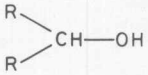
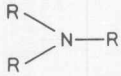
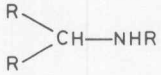
sec-Alkyl alcohol 

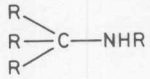
Alkyl aldehyde RCH_2CHO

Alkyl amide 

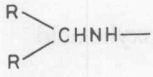
Alkyl amine RCH_2NH_2

Alkyl tert-amine 

sec-Alkyl amine 

tert-Alkyl amine 

Alkylamino $RCH_2NH—$

iso-Alkylamino 

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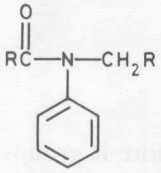

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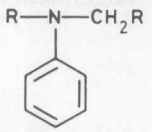

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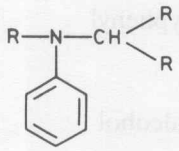

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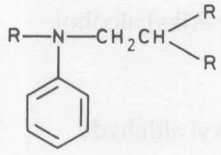

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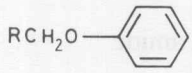

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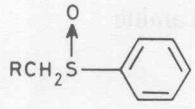

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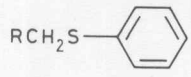

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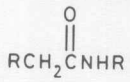

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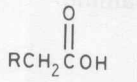

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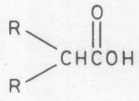

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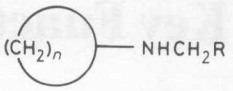

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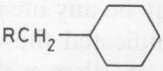
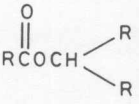


Alkyl ester

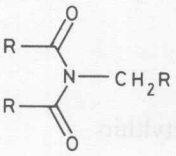
iso-Alkyl ester



Alkyl ether

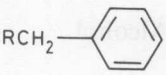
Alkyl hydrazine

N-Alkyl imide



Alkyl ketone

Alkylphenyl



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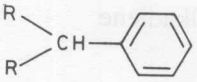

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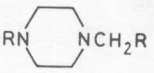

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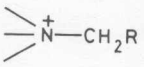
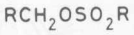


Alkyl sulphate

Alkyl sulphonate

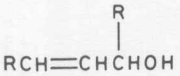


Alkyl sulphoxide

Alkyl thioether

Allyl amine

Allylic alcohol



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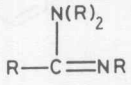

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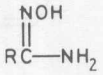
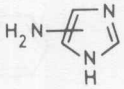


Amino acid

Aminoimidazole



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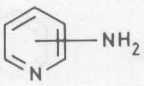

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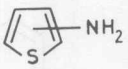

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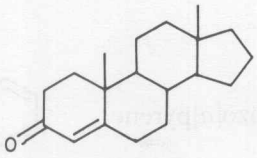

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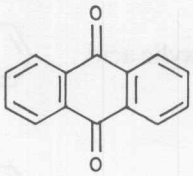

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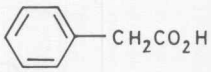

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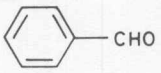

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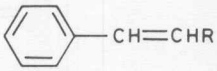

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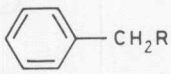

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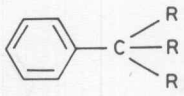

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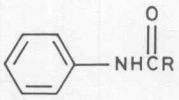

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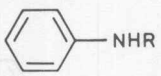

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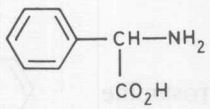
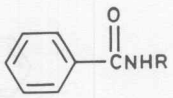
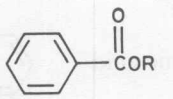
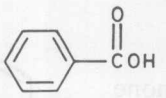


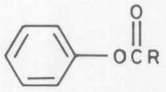
Aryl carboxamide

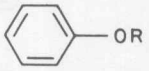


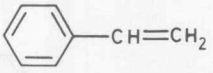
Aryl carboxylate

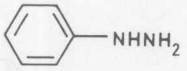


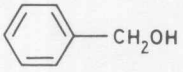
Aryl carboxylic acid 

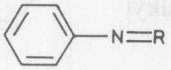
Aryl ester 

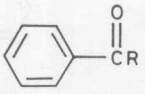
Aryl ether 

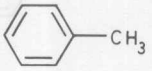
Arylethylene 

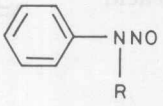
Aryl hydrazine 

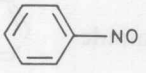
Arylhydroxymethyl 

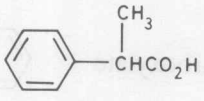
N-Arylimine 

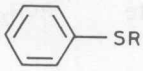
Aryl ketone 

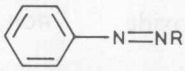
Arylmethyl 

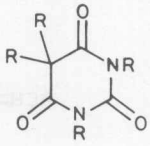
N-Arylnitrosamine 

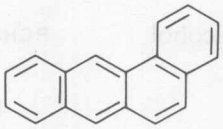
Arylnitroso 

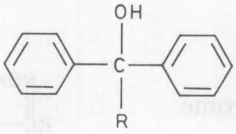
Aryl propionic acid 

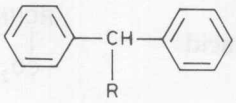
Aryl thioether 

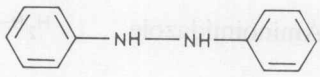
Azobenzene 

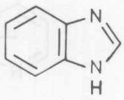
Barbiturate 

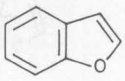
Benzanthracene 

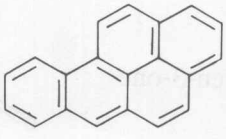
Benzhydrol 

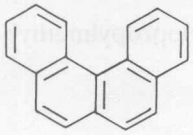
Benzhydryl 

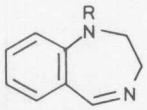
Benzidine 

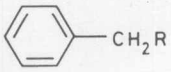
Benzimidazole 

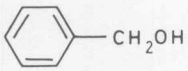
Benzofuran 

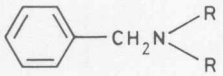
Benzo[*a*]pyrene 

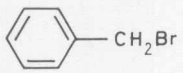
Benzo[*c*]phenanthrene 

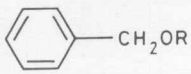
Benzodiazepine 

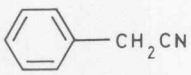
Benzyl 

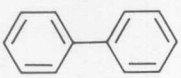
Benzyl alcohol 

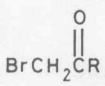
Benzyl amine 

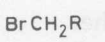
Benzyl bromide 

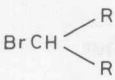
Benzyl ether 

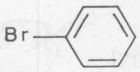
Benzyl nitrile 

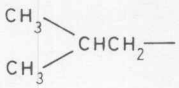
Biphenyl 

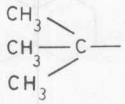
Bromoacetyl 

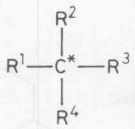
Bromoalkane 

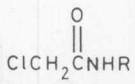
Bromoalkyl 

Bromophenyl 

iso-Butyl 

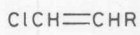
tert-Butyl 

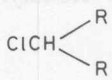
Chiral carbon 

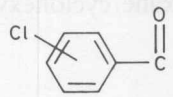
Chloroacetamide 

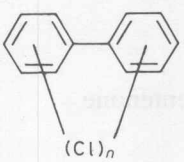
Chloroacetyl 

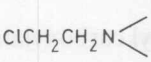
Chloroalkane 

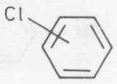
Chloroalkene 

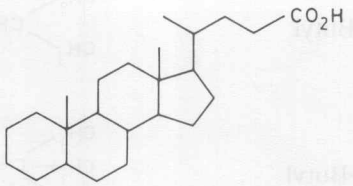
Chloroalkyl 

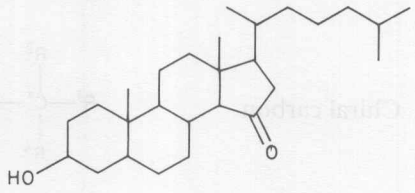
Chlorobenzoyl 

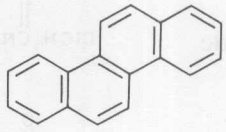
Chlorobiphenyl 

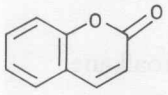
N-Chloroethyl 

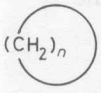
Chlorophenyl 

Cholanic acid 

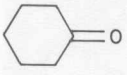
Cholestenone 

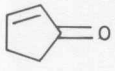
Chrysene 

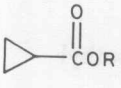
Coumarin 

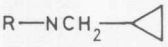
Cycloalkane/cycloalkyl 

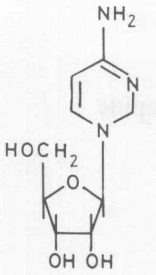
Cyclohexane/cyclohexyl 

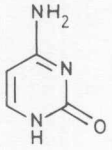
Cyclohexanone 

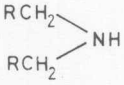
Cyclopentenone 

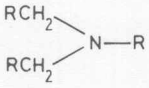
Cyclopropyl carboxylate 

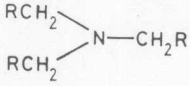
N-Cyclopropylmethyl 

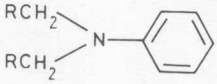
Cytidine 

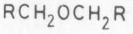
Cytosine 

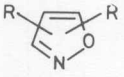
Dialkyl amine 

Dialkylamino 

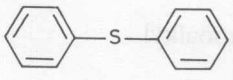
Dialkylaminoalkyl 

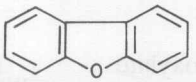
Dialkyl aryl amine 

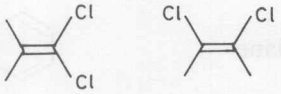
Dialkyl ether 

Dialkylisoxazole 

Dialkyl thioether

Diaryl thioether 

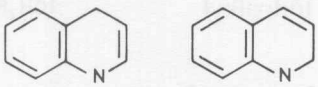
Dibenzofuran 

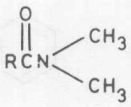
Dichloroalkene 

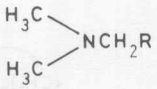
Digitoxigenin —

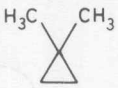
Dihydropyran 

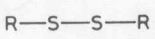
Dihydropyridine 

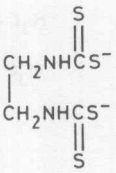
Dihydroquinoline 

Dimethylamide 

Dimethylaminoalkyl 

Dimethylcyclopropyl 

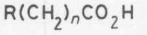
Disulphide 

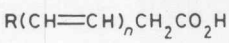
Dithiocarbamate 

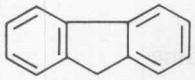
Dithiolane 

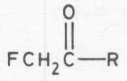
Epoxide 

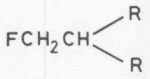
Ethynyl 

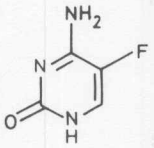
Fatty acid (saturated) 

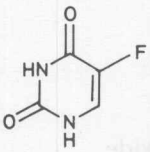
Fatty acid (unsaturated) 

Fluorene 

Fluoroacetyl 

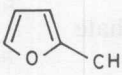
Fluoroalkyl 

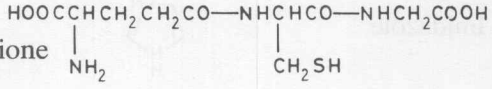
Fluorocytosine 

Fluorouracil 

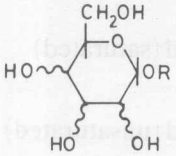
Formamide 

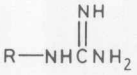
Furan 

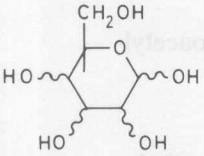
Furfural 

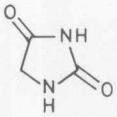
Glutathione 

Glycolamide 

Glycoside 

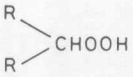
Guanidine 

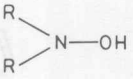
Hexose 

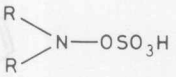
Hydantoin 

Hydrazide 

Hydrazine 

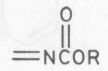
Hydroperoxide 

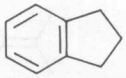
N-Hydroxy 

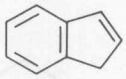
N-Hydroxy sulphate 

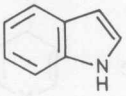
Imidazole 

Imidazoline 

Iminecarboxylate 

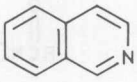
Indane 

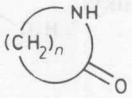
Indene 

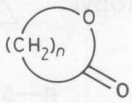
Indole 

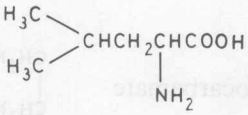
Iodoalkyl

Isoprenoid —

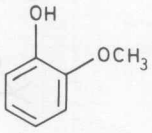
Isoquinoline 

Lactam 

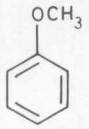
Lactone 

Leucine 

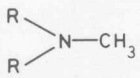
Methanesulphonate 

o-Methoxyphenol 

Methoxyphenyl

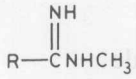


N-Methyl alkyl amine



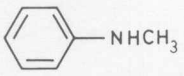
Methyl amide

N-Methylamidine



Methylamino

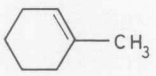
N-Methyl aryl amine



Methyl carbamate

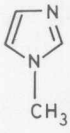
Methyl carboxylate

Methylcyclohexene

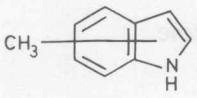


Methyl ether

N-Methylimidazole

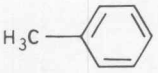


Methylindole

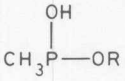


N-Methylnitrosamine

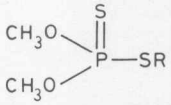
Methylphenyl



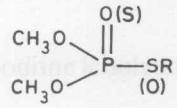
Methylphosphinoyl



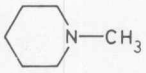
O-Methylphosphorodithioate



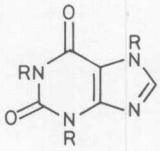
O-Methylphosphorothioate



N-Methylpiperidine

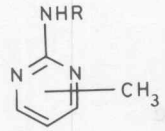


N-Methylpurine



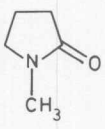
R=H or CH_3

Methylpyrimidine

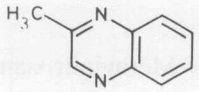


N-Methylpyrrolidine

N-Methylpyrrolidone



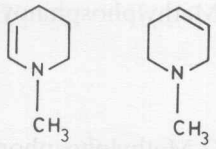
Methylquinoxaline



Methyl sulphonate

Methylsulphinyl

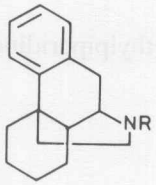
N-Methyltetrahydropyridine



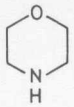
Methyl thioether

Monoclonal antibody

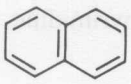
Morphinan



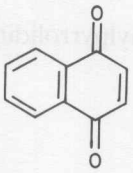
Morpholine



Naphthalene

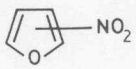


Naphthaquinone

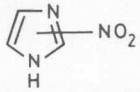


Nitrile

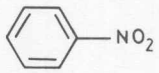
Nitrofuran



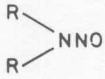
Nitroimidazole



Nitrophenyl

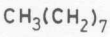


Nitrosamine

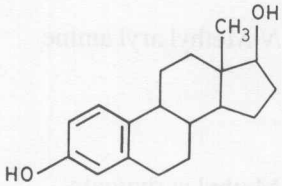


Nucleoside

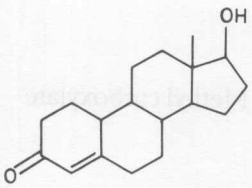
Octyl



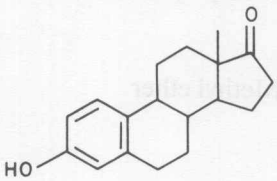
Oestradiol



Oestren-3-one

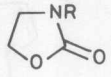


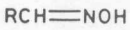
Oestrone

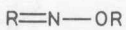


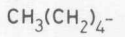
Organoarsenic

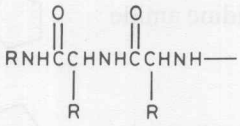
Oxazole

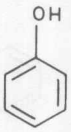
Oxazolidinone 

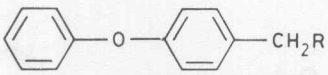
Oxime 

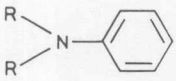
Oximino 

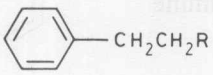
Pentyl 

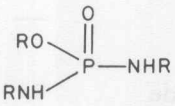
Peptide 

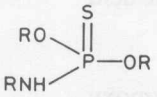
Phenol 

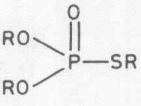
Phenoxybenzyl 

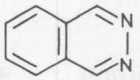
N-Phenyl 

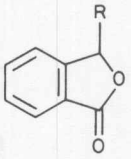
Phenylethyl 

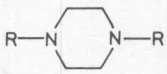
Phosphoramide 

Phosphoramidothioate 

Phosphorothioate 

Phthalazine 

Phthalidyl 

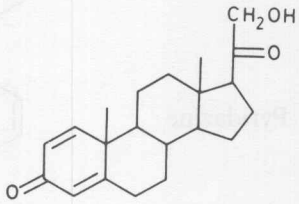
Piperazine 

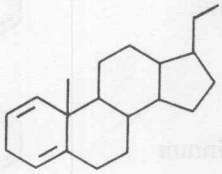
Piperidine 

Piperidinedione 

Polycyclic aromatic —

Polycyclic aromatic amine —

Prednisolone 

Pregnadiene 

Pregnene