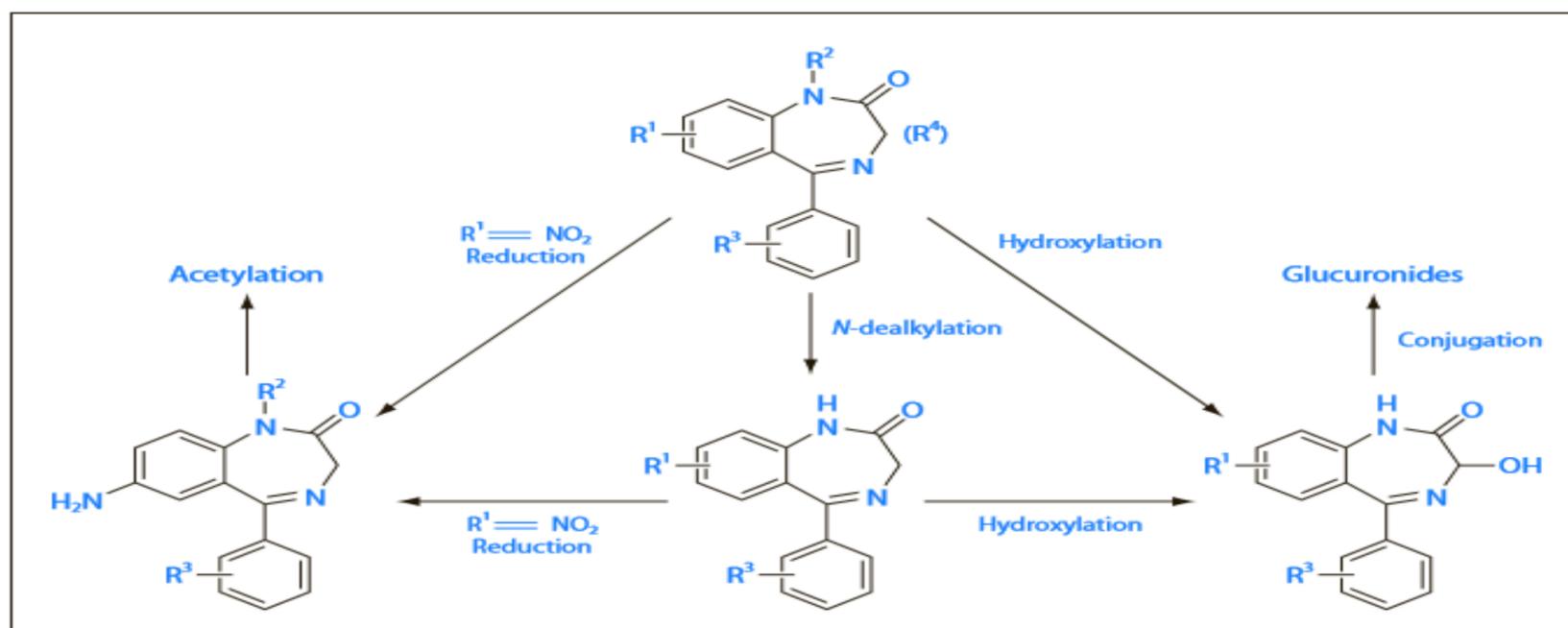


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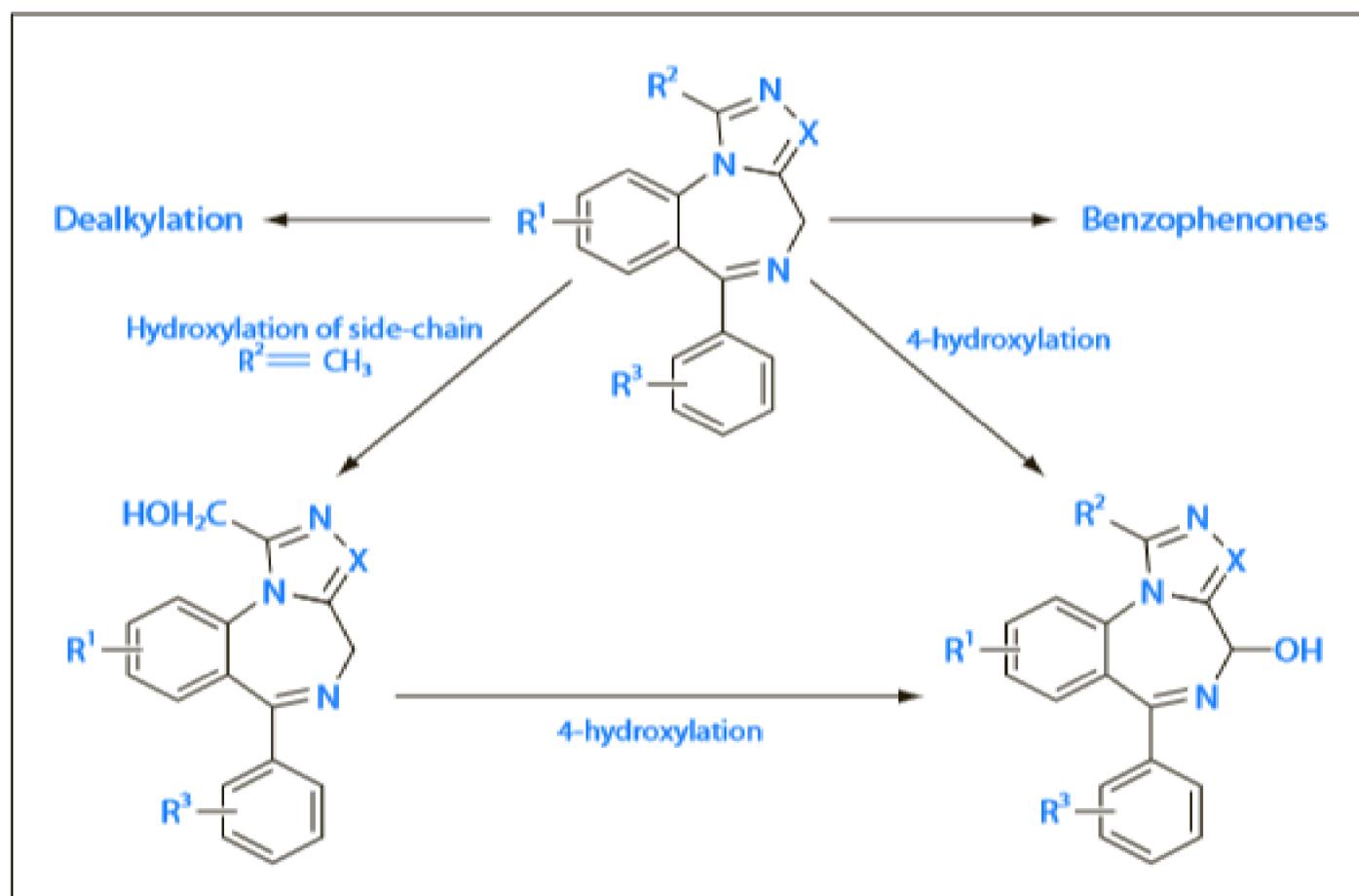
## **Benzodiazepines**

- The benzodiazepines are one of the most widely prescribed groups of drugs and are frequently found in toxicological cases.
- They undergo extensive metabolism by N-dealkylation, hydroxylation and conjugation pathways.
- Many of the metabolites of diazepam show pharmacological activity, including desmethyldiazepam (nordiazepam), 3-hydroxydiazepam (temazepam) and desmethyl-3-hydroxydiazepam (oxazepam).
- Ring-substituted benzodiazepines based on the triazolam structure show much higher potency than the first-generation benzodiazepines based on chlordiazepoxide and diazepam .
- These also include midazolam and alprazolam. For example, triazolam is one of the most potent members in active use, with daily doses starting at 0.125mg. By comparison, a typical dose for diazepam is 5–10mg, and for chlordiazepoxide it is 100mg.
- Administrative doses (including overdose) need to be taken into account when developing methods of analyses for drugs and their metabolites.
- Methods with higher sensitivity need to be used for these higher-potency drugs because the metabolites are likely to be present at much lower levels in blood and urine.
- Benzodiazepines that do not belong to these two classes are still likely to be metabolised by the same routes.
- The atypical benzodiazepine chlordiazepoxide is metabolised by demethylation and deamination to desmethylchlordiazepoxide and demoxepam.
- Demoxepam is further metabolised to nordiazepam by hydrolysis and cleavage of the lactam ring.
- The pharmacokinetic half-lives of benzodiazepines are used largely to determine their principal medical use.

- Benzodiazepines with a relatively short half-life are used predominantly as hypnotics and as supplements to preoperative anaesthesia, whereas the longer acting benzodiazepines (such as diazepam) are used as minor tranquillisers (anxiolytics).
- The urine usually contains extensive metabolites of benzodiazepines, often with little parent drug present. It is essential to know the individual metabolites of target benzodiazepines when assessing the urine of persons exposed to this class of drug.
- The clearance of benzodiazepines is decreased by liver disease, although the greatest effects occur with those drugs metabolised by the P450 system.
- Lorazepam and oxazepam, and other similar drugs metabolised by glucuronidation, are least affected. Kidney disease particularly affects benzodiazepines metabolised to active drugs and those that show a high degree of protein binding.
- Advanced age has similar effects to liver and kidney disease because of the reduction in output of major organs and changes in the volume of distribution.
- Doses of sedatives are usually halved in the elderly (>65 years), although oxazepam, lorazepam and temazepam are least affected by age.



**Figure 2.4** Metabolic scheme for 1,4-benzodiazepines. (Note: For flunitrazepam, where *N*-dealkylation is followed by reduction, R<sup>2</sup> = H.)



2.5 Metabolic scheme for diazolo- and triazolobenzodiazepines.

## BENZODIAZEPINES

Sl No	Poison	Metabolite	
1.	Diazepam	Oxazepam	1. U.V. abs in 2N HCl. Max = 242 mu & 287 mu 2. T.L.C., Dragendorff spray
2.	Chlorazepam	Lactum derivative oxazepam	1. U.V. abs in 0.1N NaOH. Max = 243 mu 2. T.L.C., Iodoplatinate spray
3.	Oxazepam	Glucuronide conjugate	1. U.V. abs in ethanol, Max = 230 mu 2. T.L.C., Dragendorff spray
4.	Nitrazepam	7-amino metabolite and 7-acetylamino metabolite	1. U.V. abs in ethanol, Max = 218 mu & 260 mu 2. T.L.C., Dragendorff spray

Reagent	Preparation of Reagent	Colour Observed	Class of Compound Present
Formaldehyde – Sulphuric Acid	4 parts of sulphuric acid + 6 parts of formalin	Red/Pink/Blue/violet/ Red-violet/Blue- violet	Benzodiazepines /Phenothiazine