Reduction and conjugation reactions of N-oxides

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1. This chapter is an overview on the further metabolism of N-oxygenated metabolites of tertiary amines, e.g. N-oxides.
2. There are three options open to N-oxygenated intermediates – further oxidation, reductions and conjugations, all of which may either be enzymic or non-enzymic. N-Oxides undergo enzymic reductions, and some are conjugated. Additionally they undergo non-enzymic rearrangements, even under physiological conditions.
3. Reductive metabolism of N-oxides in vivo may lead to futile recycling of the parent compound. Nitrogenous compounds that undergo this reversible oxidation/reduction may, therefore, have long half-lives. Some drugs may be designed as N-oxygenated pro-drugs (e.g. N-oxides, nitro compounds), that undergo selective bioreductions (activation) under anaerobic conditions in appropriate target tissues (e.g. tumours).
4. Conjugation of certain types of N-oxygenated compounds (e.g. hydroxamic acids) is now well established, and such reactions are known to confer unusual reactivity on the products formed towards cellular macromolecules. More recently, novel N-oxide conjugations (O-sulphations) have also been described for some heteroaromatic N-oxides; the implications of such reactions to drug pharmacology and toxicology are discussed, although it is not as yet clear whether this is a general route of metabolism for all types of N-oxides.
In the biological oxidation of nitrogen functionalities in xenobiotics, two processes are discernible – those where there is removal of electrons and protons, and those where there is addition of oxygen. This chapter is restricted to the further metabolism of products of the latter process, i.e. N-oxygenated compounds, in particular the N-oxides. Such compounds may be produced as oxygenated metabolites of nitrogenous compounds, e.g. N-oxides, hydroxylamines, hydroxamic acids etc. (Damani, 1982; Hlavica, 1982; Gorrod and Damani, 1985; Cho and Lindeke, 1988). Alternatively, N-oxo functionalities may be present in synthetic or biosynthetic drug and other xenobiotics molecules (Jenner, 1978). The presence of an N-oxo group in a drug molecule may be a deliberate design feature, with bioreduction in appropriate target tissues as an activation process. Whereas a considerable amount of data has now accumulated on nitrogen oxidation (see Bridges et al., 1972; Gorrod, 1978; Gorrod and Damani, 1985 and references cited therein), the further metabolism of the N-oxygenated intermediates has not been studied as extensively or systematically. In particular, the reversible nature of certain N-oxygenations under physiological conditions in vivo has not been fully established. However, a clear understanding of the role of N-oxidation of nitrogenous compounds in vivo is only possible if the contribution of metabolically reversible reactions is fully appreciated.

The metabolic options available to any N-oxygenated compound are determined by the chemical nature of the functional group and the oxidation state of the constituent nitrogen. In general there are three options; (1) further oxidation to an N-oxygenated metabolite with the nitrogen in a higher oxidation state, e.g. oxidation of an arylhydroxylamine (Ar-NHOH, oxidation state -1) to an arynitroso metabolite (Ar-NO, oxidation state +1); (2) reduction of the N-oxygenated functionality, e.g. reduction of N-oxides (oxidation state -1) to the parent tertiary amines (oxidation state -3); (3) conjugation at the N-oxygenated groups, e.g. N-O-glucuronidation, or direct N-glucuronidation of arylhydroxylamines. This review only addresses the latter two options, i.e. reductions and conjugations of N-oxides. These further transformations may in some instances be non-enzymic, occurring in vivo or in vitro or during sample storage/analysis due to the instability of the N-oxygenated intermediate, e.g. non-enzymic aliphatic N-oxide reductions during sample analysis (Chapter 3). Even when these reactions are biotransformations, they need not always be mediated by mammalian enzyme systems. In many instances the microbial flora in the gastrointestinal tract plays a significant role in the bioreduction of N-oxygenated compounds. Reductions and conjugations, and subsequent hydrolysis of the conjugates by microflora, afford the opportunity for metabolic recycling. These reversible processes un-