Cyclisation of an Amine Oxide Initiated by Successive Redox Reactions

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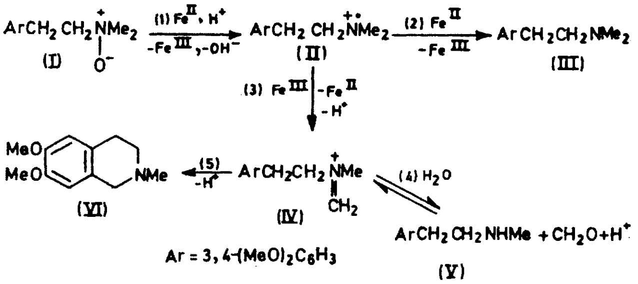
Summary 3,4-Dimethoxy-*NN*-dimethylphenethylamine *N*-oxide reacts with iron(II) ion to give the corresponding tertiary amine, the demethylated secondary amine, and 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline in relative amounts which depend, in a way which has been rationalised, upon the reaction temperature and time, the presence of a base, and the concentration of iron(II).

IT has been suggested that tertiary amine oxides mediate both in the metabolic dealkylation of tertiary amines[1] and in the formation of heterocyclic rings in the biogenesis of certain alkaloids,[2] and the chemical feasibility of both processes has been indicated by a study of the behaviour of 3,4-dimethoxy-*NN*-dimethylphenethylamine *N*-oxide towards sulphur dioxide.[3] In this case the processes apparently involve entirely two-electron steps, and we have now found that the transformations can also be initiated by consecutive one-electron steps; thus, the use of an iron(II)–iron(III) couple has given results consistent with the mechanisms in the Scheme.

The conversion of a number of tertiary amine oxides into mixtures of tertiary and secondary amines has previously been effected by iron(II) ion; there is evidence that aminium radical cations and immonium ions corresponding to (II) and (IV) are involved.[4] When similar conditions (*ca.* 0·25M-sulphuric acid under reflux) were applied to the *N*-oxide (I), only the tertiary amine (III) was obtained. However, the inclusion of a base (*e.g.*, ammonia, pyridine, 2,2′-bipyridyl, or 2,6-lutidine) resulted in the formation of products (V) and (VI) as well. The base may act not only to facilitate reaction (3) but also, through its capacity as a ligand, to modulate the relative ease of one-electron reduction and oxidation of the intermediate (II); thus, under otherwise identical conditions [0·13M-iron(II), 0·05M-(I), 24 h at reflux temperature, pH 5·8], the yields of products (III), (V), and (VI) were 43, 31, and 10% with pyridine and 49, 11, and 9% with 2,6-lutidine. Pyridine was used in subsequent studies.

Increase in the reaction time to 70 h caused no change in the yield of tertiary amine, but the yield of cyclised product (VI) increased to 20% at the expense of secondary amine (also 20%). This suggested that the cyclised product is formed, relatively slowly, from the secondary amine by reaction with formaldehyde, that is, the reverse of step (4), followed by step (5); in accord with this, reaction for 30 min gave 21% of secondary amine and no cyclised product (see later). Confirmatory evidence was obtained by inclusion of the secondary amine (V; >95% CHD_2 for Me) in the reaction mixture, for 28 ± 1% of the tetrahydroisoquinoline which was then isolated contained two deuterium atoms. This mode of formation of the product (VI) is evidently ineffective at room temperature, since secondary amine but no cyclised product was obtained after 5 days under otherwise identical conditions; this is consistent with the evidence that, when generated with the aqueous sulphur dioxide system at room temperature, cyclisation of the immonium ion (IV) does not compete effectively with its solvolysis.

According to the Scheme, the combined yields of products (V) and (VI) should increase relative to that of (III) as reaction proceeds and iron(III) builds up at the expense of iron(II), or as the initial concentration of iron(II) is reduced from an excess with respect to the *N*-oxide to a catalytic amount. These expectations were borne out in practice; under otherwise identical conditions, reduction in the reaction time from 24 h to 30 min afforded approximately the same yield of (III) (43%) but a reduction in the yields of (V) + (VI) from 41 to 21%, while a twenty-fold decrease in the concentration of iron(II) caused the yields of (III) and (V) + (VI) after 24 h to change from 43 and 41%, respectively, to 17 and 54%.



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