Reduction and Dehydrative Cyclisation of Amine Oxides

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Summary Sulphur dioxide reduces 3,4-dimethoxy-*NN*-dimethylphenethylamine *N*-oxide mainly to the corresponding tertiary or secondary amine in acetic acid or water respectively, but principally effects dehydrative cyclisation to 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline in formic acid.

TERTIARY AMINE OXIDES have been suggested as intermediates in the metabolic dealkylation of tertiary amines[1] and in the formation of heterocyclic rings during alkaloid biogenesis.[2] Our studies of the reactions of 3,4-dimethoxy-*NN*-dimethylphenethylamine *N*-oxide (I) (Ar = 3,4-dimethoxyphenyl throughout) with sulphur dioxide indicate the feasibility of both processes.

Reaction in water for 1 hr. at room temperature gave 8% of the amine–sulphur trioxide adduct,[3] 18% of the tertiary amine (III), and 46% of the secondary amine (V) (*cf.* reaction between trimethylamine *N*-oxide and sulphur dioxide[3]), whereas in acetic acid only the tertiary amine (III) was isolated (48%). We suggest the mechanism shown, according to which the relative amounts of secondary and tertiary amine are determined by partitioning of the adduct (II); since the generation of the immonium ion (IV), and hence secondary amine, involves the separation of opposite charges whereas that of the tertiary amine involves the disappearance of these charges, relatively less of the secondary amine would be expected on reduction of the ionising power of the solvent, as observed.

We argued that a solvent whose ionising power was comparable with, but whose nucleophilicity was sufficiently less than, that of water might favour formation of the immonium ion (IV) while inhibiting its subsequent solvolysis, thereby allowing it to be trapped by intramolecular cyclisation. Formic acid is such a solvent,[4] and its use afforded 61% of the tetrahydroisoquinoline derivative (VI) together with 29% of the tertiary amine (III).

To test the applicability of this reaction, we examined the behaviour of three other amine oxides towards sulphur dioxide in formic acid, finding that cyclisation occurred in each case but only through the immonium ion derived from the *N*-methyl group. Thus, laudanosine *N*-oxide gave norcoralydine (14·5%), bis-(3,4-dimethoxyphenethyl)-*N*-methylamine *N*-oxide gave 1,2,3,4-tetrahydro-6,7-dimethoxy-2-(3′,4′-dimethoxyphenethyl)isoquinoline (40%), and *NN*-dimethyltryptamine *N*-oxide gave 1,2,3,4-tetrahydro-2-methyl-β-carboline (58%).

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