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The Reaction of Erythromycin Hydrazone with Nitrous Acid
A New Route to Erythromycylamine

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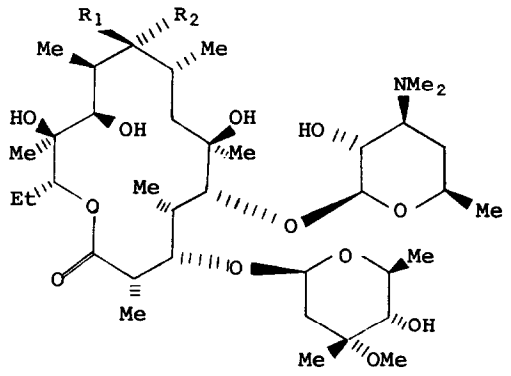
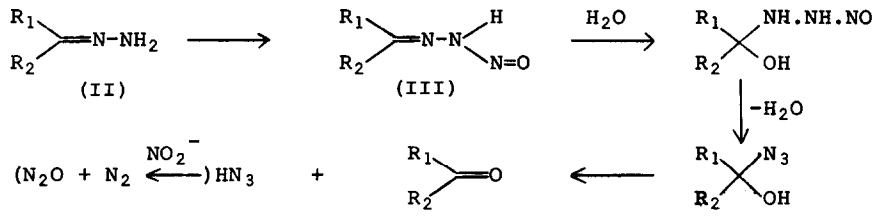
In the course of a search for a practical route to the antibiotic erythromycylamine (I, R_1 = NH_2, R_2 = H) an unusually stable imine (I, R_1R_2 = =NH) was isolated from the reaction of erythromycin oxime (I, R_1R_2 = =NOH) with titanium trichloride.[1] This communication records a second route to this imine and reveals a new pathway for the reaction of hydrazones with nitrous acid.



(I)

Treatment with nitrous acid has been used[2-4] to convert hydrazones to the parent carbonyl compounds and in one case (II, R_1 = Acyl, R_2 = H) the following mechanism has been suggested:-[2]



The feasibility of this scheme is supported by the isolation of α-azido ethers when the corresponding reaction is carried out in alcoholic solvent.

In contrast, reaction of erythromycin hydrazone (I, R_1R_2 = =N-NH_2) with sodium nitrite (pH 4; 8-10°) proceeds with evolution of nitrous oxide and gives an almost clean (t.l.c.) conversion to erythromycin imine identical to that obtained by reduction of the oxime with $TiCl_3$.[1] This imine may be isolated or reduced *in situ* to the desired amine by $NaBH_4$ at pH ∿ 8. This sequence provides a route to erythromycylamine in kilogram quantities.

Thus there is available a second mode of reaction in which intermediate III, or a tautomer thereof, eliminates a molecule of nitrous oxide directly:

Elimination of N_2O is observed on nitrosation of *unsym*-disubstituted hydrazines where the azidohydrin route is not available.[5] That this pathway is preferred on nitrosation of erythromycin hydrazone is reasonable in view of the very low susceptibility of the trigonal carbon atom at C-9 of erythromycin and its derivatives to nucleophilic attack.[1] Thus azidohydrin formation is unfavourable and the alternative pathway becomes dominant.

It is clear that in some cases direct elimination of nitrous oxide and azidohydrin formation may be competitive pathways for the reaction of hydrazones with nitrous acid.

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