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CONVERSION OF 9-SUBSTITUTED ADENINES TO THE CORRESPONDING PURINES

A SIMPLE DEAMINATION METHOD FOR ADENINE DERIVATIVES

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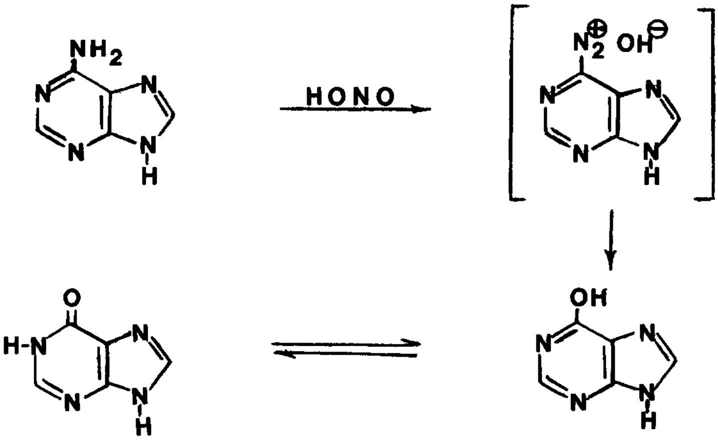
Summary: An effective procedure for the replacement of an amino group in nucleic acid bases with hydrogen is described. The method provides a direct synthesis of the antibiotic, nebularine, from adenosine.

Although the deamination of aromatic amines with replacement by hydrogen of the amino group has been accomplished in numerous systems,[1] such diazotization-deamination reportedly fails under a variety of conditions for 6-aminopurine (adenine) derivatives.[2-4] While 6-diazonium salts of purine have never been isolated, conversion of adenine to hypoxanthine in nitrous acid (Scheme 1)[5] and of 6-aminopurine derivatives to 6-fluoropurines[6,7] are presumptive of diazonium intermediates where the counterion also acts as a nucleophile. We now wish to

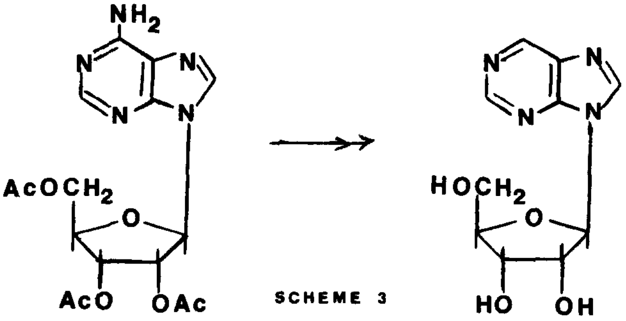


SCHEME 1

report the successful deamination of 9-substituted 6-aminopurines under mild conditions to give the corresponding purines, and extension of this method to the synthesis of the antitumor antibiotic, 9-β-D-ribofuranosylpurine (nebularine)[8] from adenosine.

We utilized in this deamination the known ability of alkyl nitrites to produce aryl radicals from arylamines and the subsequent possibility of hydrogen abstraction by the radical from a suitable hydrogen atom donor.[9,10] The latter can be the solvent. Of the various solvents or solvent combinations with potentially abstractable hydrogen atoms, we found dry tetrahydrofuran to be the most satisfactory. As radical processes are inhibited by the presence of scavengers such as O_2 or NO, the solvent was initially purged with nitrogen and the reaction was conducted in an atmosphere of nitrogen Diazonium salts and azo compounds (which predominate in neutral solution) are decomposed homolytically by blue light,[11] so irradiation to aid homolytic dissociation was also included Thus when a solution of 9-ethyladenine in dry distilled THF was treated with n-pentyl nitrite under nitrogen and refluxing temperatures and with constant illumination from a 200 watt tungsten filament lamp for 6 hr, chromatographic separation of the product mixture gave 9-ethylpurine in 68% yield (Scheme 2). The structure of the product was confirmed by ^{13}C, ^{1}H NMR and UV spectroscopic data comparison with an authentic sample prepared from sodium purinide and ethyl tosylate [12,13] Interestingly, no coupling products or hypoxanthine were detected 9-Benzyladenine was similarly deaminated to the corresponding purine in good yield.

SCHEME 2



SCHEME 3

In order to examine the generality of this deamination method, we extended the study to nucleosides Thus when 2',3',5'-tri-O-acetyladenosine in THF was deaminated as described above, 2',3',5'-tri-O-acetylnebularine was isolated in 41% conversion. The protected compound can be converted easily to nebularine by deacylation with methanolic ammonia (Scheme 3). This represents an excellent direct synthesis of this nucleoside antibiotic from readily available adenosine [14-16] We are currently examining the application of this simple deamination method to the synthesis of more complex modified nucleosides

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