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REDUCED ADENINES REDUCTION OF ADENINES WITH BOROHYDRIDE

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Although reduced adenines are of interest from the biological viewpoint,[1,2] they have not been generally well-known derivatives

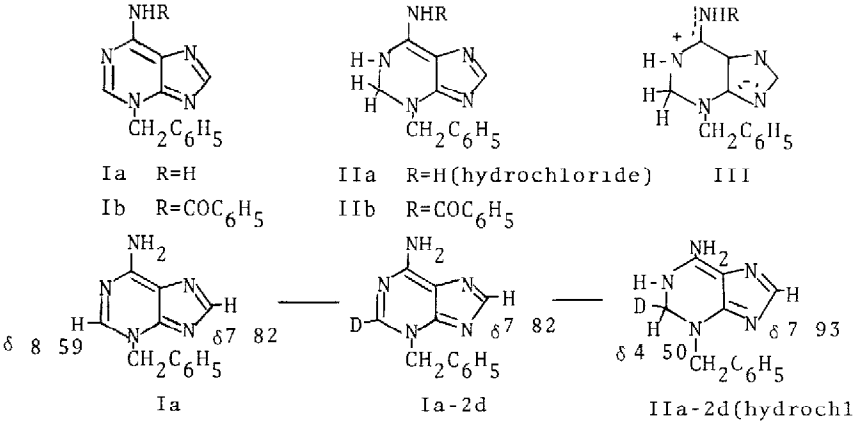
Smith and Elving[3] have reported that electrochemical reduction of adenines occurs across the 1,6-double bond and subsequently causes elimination of ammonia Macon and Wolfenden[4] have studied borohydride reduction of 1-methyladenosine, a minor base of t-RNA, taking aim at its modification, i e , The reduction at pH 8 2 resulted in the formation of 1-methyl-1,6-dihydroadenosine which underwent easily reoxidation In these previous studies, the reduced adenines have never been isolated in the pure state

The present communication describes first isolation and characterization of dihydroadenines formed by the reduction of 3- and 9-substituted adenines with sodium borohydride We found that the presence of N-benzoyl grouping and the reaction medium employed significantly affect on the reduction, and the isolated dihydroadenines are stable under the usual conditions It is particularly notable that N-benzoyl-9-substituted adenines gave 7,8-dihydroadenines rather than expected 1,6-dihydroadenines by virtue of the reduction in the acidic medium

Chemical evidence[5] has indicated that the introduction of alkyl grouping at the ring-nitrogen on the pyrimidine portion of purines causes apparent π-deficiency of the pyrimidine ring Thus, the pyrimidine ring of benzyladenines(Ia and Ib) could be susceptible to the reduction with borohydride

To a stirred solution of (Ib)(1 mol) in methanol, sodium borohydride(1 5 mol) was added by portions at room temperature After stirring for 30 min, a mixture was concentrated to leave an oily residue which was treated with water and extracted with chloroform. The extract was submitted to column chromatography(Al_2O_3-$CHCl_3$) to isolate N-benzoyl-3-benzyl-1,2-dihydroadenine(IIb)[6] as

colorless crystals(70%, mp 161°) Bathochromic shift of the UV spectrum[UV λ_{max}^{EtOH} nm(logε) 245(4 06), 283(4 00), 366(4.28)] and up-field shift of the C_8-proton signal in the NMR spectrum[NMR(DMSO-d_6)δ 7 88] compared with those of (Ib)[UV λ_{max}^{EtOH} nm(logε) 297(5.13), NMR(DMSO-d_6)δ 8 22] can be ascribed to the important contribution of the dipolar 1,3-diazafulvene structure(III) to the resonance hybrids



Scheme 1

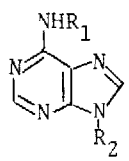
Analogously, the reduction of (Ia) was carried out In this case, however, the prolonged reaction time was required and 1,2-dihydroadenine(IIa) was isolated as its hydrochloride(40%, mp 164°) Upon treatment with pyridine-benzoic anhydride, (IIa)·HCl was converted to (IIb) together with a small amount of (Ib)

Deuterium exchange at the position 2[7] of (Ia) was achieved selectively upon treatment with boiling methanol-d_1 containing sodium methoxide for 8 hr Disappearance of a highly deshielded C_2-proton signal[8](δ8 59) of (Ia) in the NMR spectrum of the deuterated compound confirmed occurence of deuterium exchange at the position 2 of (Ia) 3-Benzyladenine-2d(Ia-2d) thus obtained was reduced in the conditions analogous to the case of (Ia) The NMR spectrum of the product (hydrochloride) showed the C_2-methylene signal atδ4 50 which was integrated to be 1H (see Scheme 1) Thus, structure(IIa)(as a consequence, structure(IIb)) was established

In addition to the electrophilic nature of the pyrimidine ring of (Ia and Ib), involvement of stable 1,3-diazafulvene skeleton in the product(IIa and IIb) appears to destine attack of a hydride ion at the position 2

9-Benzyladenine(IVa) and its N-benzoyl derivative(IVb) were inert when

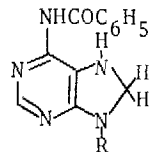
treated with sodium borohydride in alcohols More recently, Gribble et al[9] have found that sodium borohydride in neat carboxylic acids reduces the indole double bond and alkylates to give N-alkylindoline Employment of Gribble's procedure for the reduction of (IVa and IVb) seems to be advantageous, since the reduction could be facilitated as a result of protonation on the ring-nitrogen and reduced adenines produced could be stabilized by N-alkylation



IVa R_1=H, R_2=$CH_2C_6H_5$

IVb R_1=COC_6H_5, R_2=$CH_2C_6H_5$

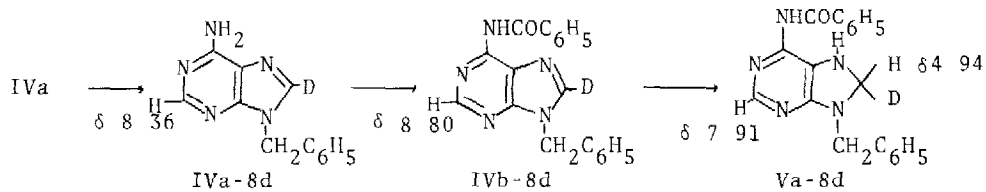
IVc R_1=COC_6H_5, R_2=2,3,5-triacetyl-β-D-ribofuranosyl



Va R=$CH_2C_6H_5$

Vb R=2,3,5-triacetyl-β-*D*-ribofuranosyl

Vc R=β-D-ribofuranosyl



Scheme 2

To a solution of (IVb)(1 mol) in acetic acid sodium borohydride(2 mol) was added by portions at room temperature After stirring for 20 min, the reaction mixture was diluted with water, extracted with chloroform, dried over anhydrous Na_2SO_4 and evaporated. The residue was recrystallized from ethyl acetate to give N-benzoyl-9-benzyl-7,8-dihydroadenine(Va)(75%, mp 184°) without N-ethylation

Occurrence of the similar reduction of N-acetyl-9-benzyladenine was also observed (checked by NMR) Isolation of the reduced product, however, did not succeed

In sharp contrast to (IVb), the reduction of (IVa) under the analogous conditions did not give any reduced product and (IVa) was recovered unchanged

Determination of reductive site of (IVb) was made by deuterium label experiment N-Benzoyl-9-benzyladenine-8d(IVb-8d) was prepared unequivocally via treat-

ment of (IVa) with methanol-d_1 containing sodium methoxide The reduction of (IVb-8d) with borohydride in acetic acid gave (Va-8d) in 70% yield The NMR spectrum of (Va-8d) showed a C_8-methylene signal apparently reduced to 1H (see Scheme 2)

N-benzoyl-2',3',5'-tri-O-acetyladenosine(IVc) was reduced under the similar conditions to give 7,8-dihydro derivative(Vb)(58%, mp 118°) Treatment of (Vb) with sodium hydroxide in a mixture of water, ethanol and pyridine at room temperature gave N-benzoyl-7,8-dihydroadenosine(Vc)(75%, mp 135°)

7,8-Dihydro-9-substituted adenines(Va,c) are stable on refluxing in alcohol and can be stored under the usual conditions

Exclusive formation of 7,8-dihydro derivatives(Va,c) rather than 1,6-dihydro derivatives from (IVb,c) is the intriguing problem Extension of present observations and biological evaluation of reduced adenines are now in progress.

References and Footnotes

1 1,6-Dihydroadenines have been posturated as an intermediate in oxidative phosphorylation of adenine nucleotides in mitochondoria(cf. V P Skalchev,Nature, 198, 444 (1963)) and also promised as a potential inhibitor of the enzymes relating to purine interconversions(cf B Evans and R Wolfenden, J. Amer Chem Soc., 92, 4751 (1970), ibid., 94, 5402 (1972))

2 For a review concerning reduced purines, see "The Chemistry of Heterocyclic Compounds", ed by A. Wissenberger and E C Taylor, Vol 24(Part II), p 427

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6 All new compounds described here gave satisfactory microanalytical results and spectral data consistent with their structures

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8 Assignment of the signal was deduced from the NMR comparison with 3-benzyladenine-8d prepared unambigously by benzylation of adenine-8d

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