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THE DIRECT UTILIZATION OF UNSATURATED SUGARS IN NUCLEOSIDE SYNTHESES. AN APPROACH TO THE PREPARATION OF ANALOGS OF BLASTICIDIN S. SYNTHESIS OF 9-(2',3'-DIDEHYDRO-2',3'-DIDEOXY-D-ERYTHRO-HEXOPYRANOSYL)GUANINE (1)

Eldon E. Leutzinger, Roland K. Robins and Leroy B. Townsend

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

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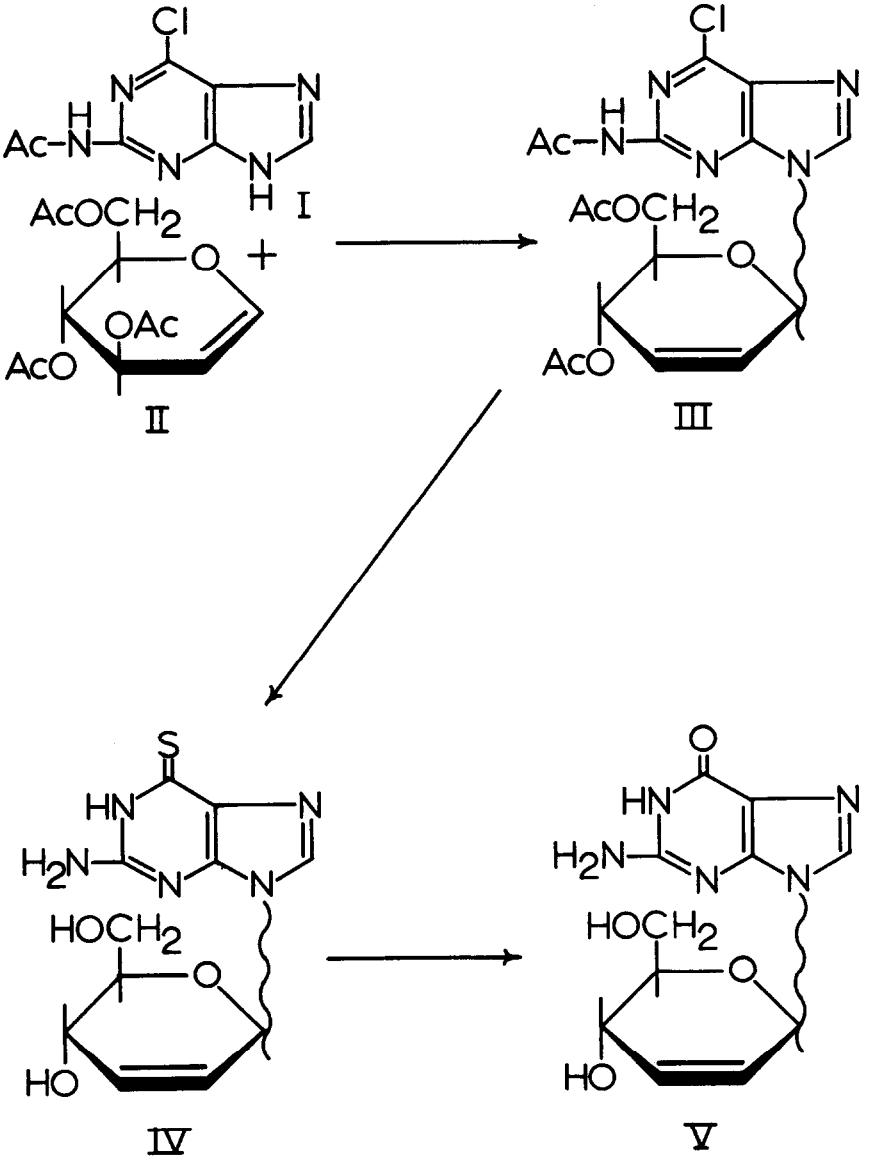
We wish to report a new procedure for the synthesis of a 9-pyranosylpurine possessing 2', 3'-unsaturation and a general synthetic approach to 2',3'-unsaturatedpyranosyl nucleosides structurally related to Blasticidin S. This procedure has been employed in the synthesis of the guanosine analog 9-(2',3'-didehydro-2',3'-dideoxy-D-erythro-hexopyranosyl)guanine (V).

The proposal (2,3) that naturally occurring ribonucleosides might be converted into deoxynucleosides via a 2',3'-unsaturated intermediate created considerable interest which resulted in the chemical preparation of several 2',3'-unsaturatedfuranosyl nucleosides (4,5) of purines and pyrimidines. The isolation (6) and recent structure elucidation (7,8) of the nucleoside antibiotic blasticidin S has revealed blasticidin S to be a pyranosyl derivative of cytosine with an endocyclic double bond at the 2',3' positions. Blasticidin S has exhibited significant antifungal activity against Piricularia oryzae in rice blast disease (9), inhibition of several transplantable animal tumors (10) and more recently has shown a definite inhibition of polypeptide synthesis (11) in an E. coli strain of B cells. A mixture of 2-acetamido-6-chloropurine (I) and 3,4-6-tri-O-acetyl-D-glucal (II) was fused at 140° in the presence of a catalytic amount of trichloroacetic acid to furnish 30% yield of a white crystalline solid (III, m.p. 103-104°). The pmr spectrum of III revealed the presence of an absorption peak at δ 2.5 (3 protons) which was assigned to the 2-acetamido group on the basis of pmr spectrum analysis of I. The absence of two additional protons at δ 2.5 indicated that the nucleoside material was not a 2'-deoxypyranoside (12). There was observed two singlet absorptions (3 protons each) in the δ 2.05-2.15 region which corresponded to acetyl groups on the carbohydrate moiety. This represented the loss of one acetyl group from II via an allylic expulsion of the C-3 acetate group (13) during nucleoside formation (14). The remaining absorption peaks in the pmr spectrum (for the carbohydrate moiety) were partially assigned utilizing a comparison of the chemical shift data [δ 6.55 (H-1', multiplet), δ 6.1-6.3 (H-2' and H-3', multiplet), δ 5.48 (one proton, multiplet) and δ 4.1-4.4 (3 protons, multiplet)]


Cl
N
H
Ac–N
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I
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OAc
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Ac–N
N
N
AcOCH2
O
AcO
III
S
HN
N
H2N
N
N
HOCH2
O
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IV
O
HN
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H2N
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N
HOCH2
O
HO
V

observed for III and the chemical shift data reported (15,16) for certain 4,6-di-O-acetyl-2,3-didehydro-2,3-dideoxy-D-erythro-hexosides. The multiplet at δ 5.48 is presumably the H-4' proton and the multiplet at δ 4.1-4.4 can be assigned to the H-5', H-6_{ax} and H-6_{eq} protons. The nucleoside product obtained from the fusion reaction was assigned the structure 2-acetamido-6-chloro-9-(4',6'-di-O-acetyl-2',3'-didehydro-2',3'-dideoxy-D-erythro-hexopyranosyl)purine (III) on the basis of the above pmr data and elemental analysis (17). The actual site of glycosidation was established in the next step. Treatment of III with a methanolic solution of sodium hydrosulfide resulted in a facile nucleophilic displacement of the 6-chloro group with a concomitant removal of the blocking groups to furnish a 41% yield of 2-amino-9-(2',3'-didehydro-2',3'-dideoxy-D-erythro-hexopyranosyl)purine-6-thione (IV); m.p. 187-188°. It was established that complete deacetylation had occurred by virtue of the absence of any absorption peaks in the pmr spectrum of IV in the δ 2.0-2.5 region. A comparison of the ultraviolet spectra of IV [$\lambda_{max}^{pH\ 1}$ 261.5 nm, 345 nm (ϵ 4600, 12000; $\lambda_{max}^{pH\ 11}$ 251.5 nm; 318 nm (ϵ 7500, 11000)]with the spectra of 2-amino-1-methylpurine-6-thione (18), 2-amino-3-methylpurine-6-thione (19), 2-amino-7-methylpurine-6-thione (20) and 2-amino-9-ethylpurine-6-thione (21) firmly established the actual site of glycosidation for IV as N-9. Thus the precursor III, is also a purine-9-glycoside. The sulfur atom at position six was exchanged for an oxygen atom by treatment of IV with hydrogen peroxide in a 20% aqueous ammonia solution to furnish a 78% yield of 2-amino-9-(2',3'-didehydro-2',3'-dideoxy-D-erythro-hexopyranosyl)purin-6-one (V) [$\lambda_{max}^{pH\ 1}$ 253 nm, 275 nm (ϵ 11500, 8200), $\lambda_{max}^{pH\ 11}$ 262 nm (ϵ12000)]. A comparison of the pmr spectrum of V with the pmr spectrum of IV revealed virtually no change in that region of the spectrum attributed to the carbohydrate moiety (δ3.0-7.0). Retention of the absorption peaks assigned to the vinylic protons (δ 6.1-6.3, multiplet) firmly established that the oxidation step had occurred without affecting the 2',3'-endocyclic double bond. Extension of the fusion procedure utilizing unsaturated sugars in novel nucleoside syntheses is an area under continuing investigation in our laboratory.

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