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C-NUCLEOSIDES AND RELATED COMPOUNDS. V.

THE SYNTHESIS OF D,L-4(1β-RIBOFURANOSYL)3-CARBOXAMIDOPYRAZOLE (V), D,L-5(1β-RIBOFURANOSYL)2-AMINO-1,3,4-OXADIAZOLE (VII) AND D,L-5(1β-RIBOFURANOSYL)3-AMINO-1,2,4-TRIAZOLE (IX).

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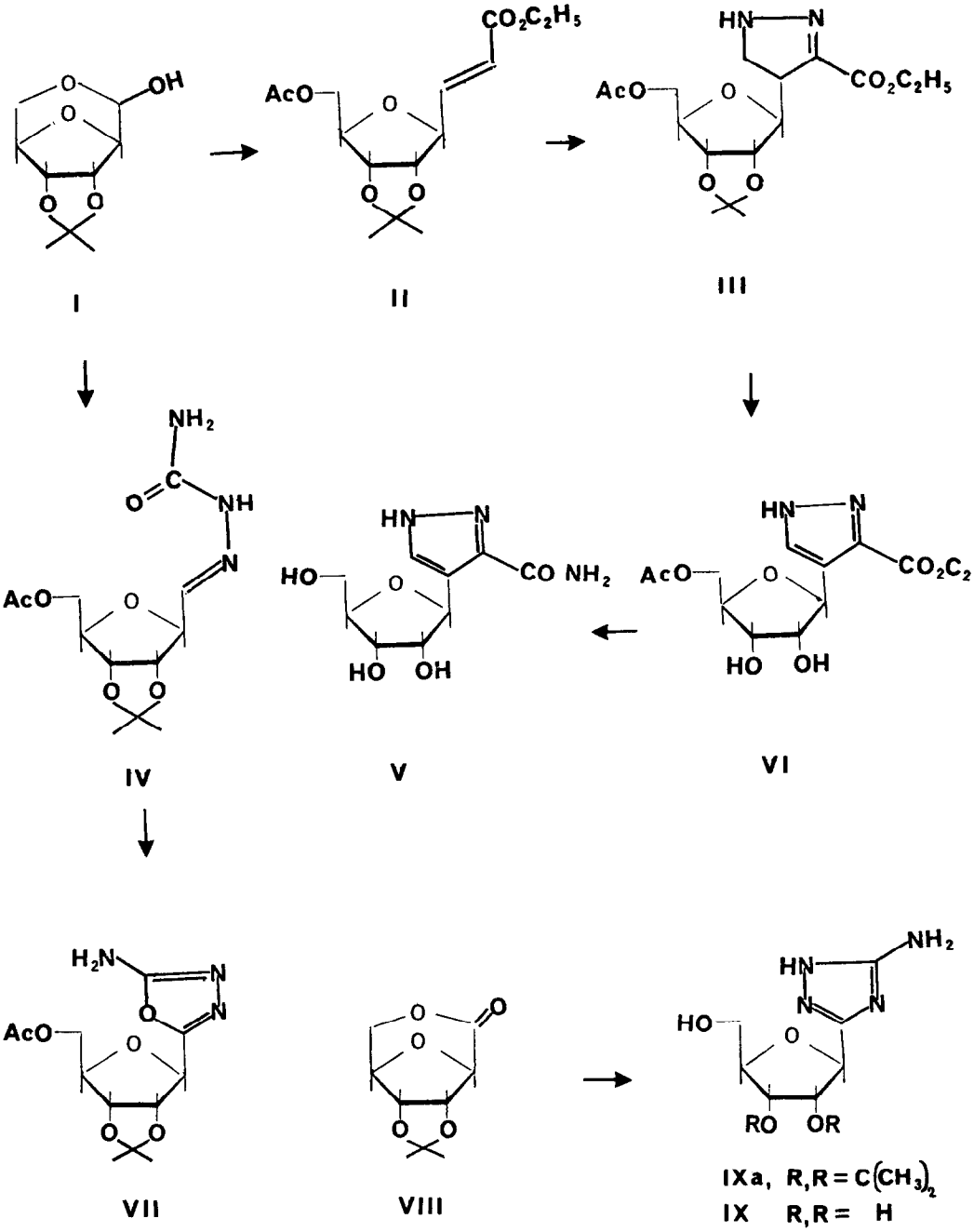
We recently described a simple and efficient synthesis of D,L-3,4-O-isopropylidene-2,5-anhydroallose (I)[1] and of the related allonic acid lactone VIII and acrylic ester II[2]. We should like to demonstrate the utility of these intermediates for the synthesis of analogues of C-nucleosides such as V, VII and IX.

For the preparation of V, an ethereal solution of acrylate II was stirred with a five fold excess of ethereal diazomethane at 25° for 18 hours. Evaporation gave pyrazoline III as a mixture of isomers[3]. Without purification, a chloroform solution of III was treated with 1.5 equivalents of bromine for one hour at 0°. The mixture was stirred with aqueous sodium sulfite for 15 minutes. Evaporation of the aqueous layer, re-extraction of the residue with ethyl acetate and purification by t.l.c. (silica gel, ethyl acetate) gave the oily VI[4], R_f .35, in 50% yield. Stirring VI with excess methanolic ammonia several days gave crystalline V[8], m.p. 208-210°, λ_{max}^{EtOH} 220 nm (ε7000), the resolved form of which was recently described by Moffat, Repke and Albrecht[5].

In order to prepare VII, semicarbazone IV[2], m.p. 148°, was treated at 0° in a nitrogen atmosphere with lead tetraacetate[6] in dry methylene chloride. Further stirring for 1 hr at room temperature, followed by the usual work-up, gave crystalline VII[8], m.p. 132°, λ_{max}^{EtOH} 230 nm (ε10,000) in 65% yield. Attempts at cleavage of the isopropylidene under various conditions always resulted in partial break-down of the oxadiazole ring.

Treatment of the lactone VIII with aminoguanidine according to the procedure of Reid and Valentin[7] gave IXa, m.p. 136°[8]. Hydrolysis of the acetonide group with trifluoroacetic acid containing 10% water for 10 minutes gave oily IX[8], λ_{max}^{EtOH} 222 nm (ε2100).

Biological tests were performed on samples of III and VI with nine


I
II
III
IV
V
VI
VII
VIII
IXa, R,R = C(CH3)2
IX R,R = H

different viruses[9] in tha agar diffusion assay and against vaccinia and herpesvirus in plague-reduction assays. No significant indication of virus inhibition was detected in the agar diffusion assay. In the plaque-reduction assays which included quantities of 5, 10, 25, 50 and 100 micrograms of compound per ml of agar overlay, no cell toxicity or plaque reduction was noted with any of the two compounds.

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8. Satisfactory infrared, proton magnetic resonance, mass spectral data, and microanalyses were obtained for all products.
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