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USE OF 5-PHOSPHO-β-D-RIBOSYL AZIDE IN A NEW DIRECT SYNTHESIS OF NUCLEOTIDES

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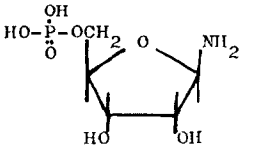
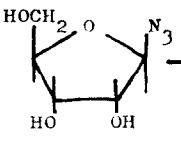
We have earlier recorded [1,2,3] general methods for the synthesis of pyrimidine and imidazole nucleosides by the reaction of glycosylamines including ribofuranosylamine derivatives, with appropriate linear precursors of these heterocyclic systems. Many of the imidazole derivatives are a convenient source of purine nucleosides. An extension of these reactions to a simple one step synthesis of analogous 5'-phosphates of wide general interest required the 5-phosphoribosylamine (I) (PRA). This compound has generally been accepted as a probable intermediate in the biosynthesis de novo of purine nucleotides [4], and solutions containing unstable material purpoted to be (I) have been formed biochemically by the reaction of 5-phospho-α-D-ribosylpyrophosphate with a suitable nitrogen donor in the presence of enzyme fractions from pigeon liver [5] (donor L-glutamine), and wheat embryos [6] (donors L-asparagine, carbamyl phosphate and ammonia). PRA is reported to be replaceable as a biochemical intermediate by the reaction product of potassium ribose-5-



I



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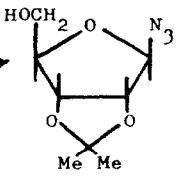

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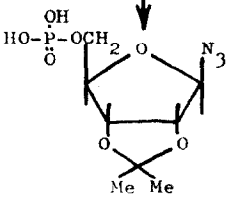

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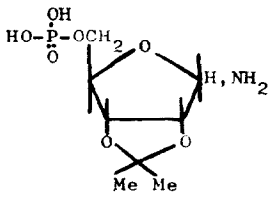

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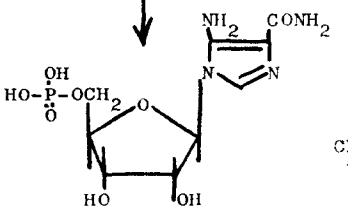


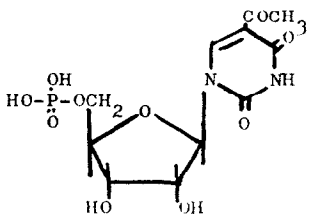
VII

EtOCH:N.CH(CN).CONH$_2$

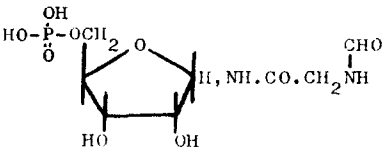
VI

$CH_3CO.C(:CHOEt).CO.NH.CO_2Et$

VIII



IX



X

phosphate and ammonia which in addition contains unreacted ribose-5-phosphate and unidentified but more stable nitrogen containing material. In our hands this synthesis gave only a substance which was not readily adaptable to further chemical reactions. We have now investigated alternate routes to more suitable derivatives of PRA.

Reaction of the ribosyl azide (II) [7] with acetone, 2,2-dimethoxy propane and "Zeo-Karb 225" resin (H^+form) gave almost quantitatively the isopropylidene derivative (III) as a colourless oil, phosphorylation of which with either β-cyanoethyl phosphate and dicyclohexylcarbodi-imide or better pyrophosphoryl chloride and pyridine in acetonitrile, gave an excellent yield of the 5'-phosphate (IV) with a well defined azide maximum at 2120 cm^{-1} as well as a peak at 1168 cm^{-1} and a doublet at 1380 cm^{-1} indicative of the gem dimethyl group.

Hydrogenation of the tri-n-octylammonium salt of (IV) at room temperature with platinic oxide and hydrogen in dry methanol resulted in loss of the azide maximum and formation of a basic compound presumably the isopropylidene derivative (V) since with the linear imidate (VI) [2] it readily gave an isopropylidene derivative from which (VII)(AICAR)[4] was obtained by mild acid hydrolysis in about 20% overall yield. The structure of this last compound was confirmed by direct comparison with an authentic sample, and by its enzymic conversion to N-(5-amino-1-β-D-ribofuranosylimidazole-4-carbonyl)-L-aspartic acid 5'-phosphate[3,4].

In a similar manner, reaction of (V) with the urethane (VIII) [3] followed by acid hydrolysis gave the pyrimidine nucleotide (IX). Also acylation of (V) with formylglycyl

chloride in dimethylformamide gave, after mild acid treatment formylglycinamide ribotide (X) [4] identical with a sample of the natural material. This is the first recorded chemical synthesis of this compound.

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