

STUDIES ON NUCLEOSIDES AND NUCLEOTIDES. III. SYNTHESIS AND REACTIONS OF
2',3'-O-(TRIPHENYL)PHOSPHORANYL-0²,5'-CYCLOURIDINE

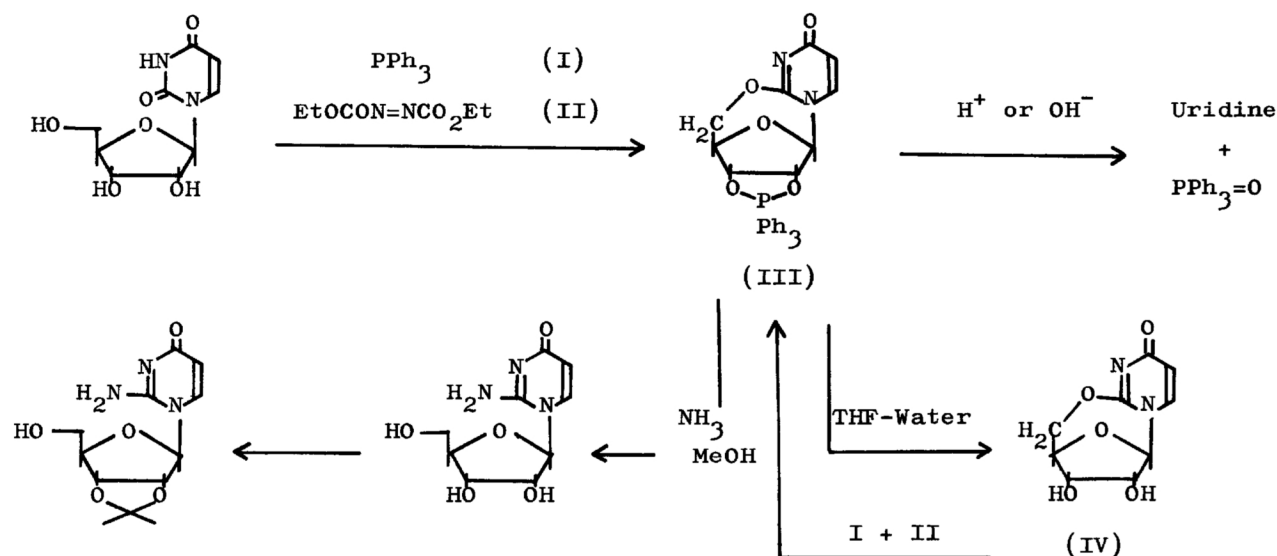
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The reaction of uridine, triphenylphosphine (I) and diethyl azodicarboxylate (II) in THF gave 2',3'-O-(triphenyl)phosphoranyl-0²,5'-cycLOURIDINE (III). The alkaline or acid hydrolysis of III gave uridine and triphenylphosphine oxide (1 : 1). The treatment of III in THF-water afforded 0²,5'-cycLOURIDINE. The reaction of III with methanol under reflux gave 0²,methyluridine.

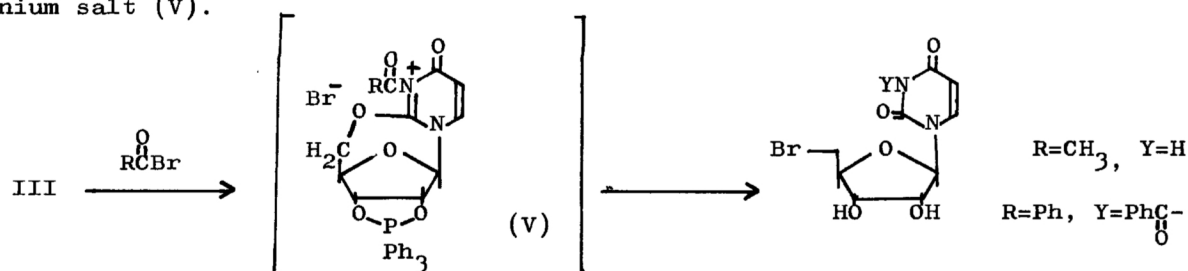
Cyclonucleosides have been used as important intermediates for the synthesis of nucleosides and nucleotides.¹ In a previous paper,² we have reported that 2',3'-O-isopropylidene-0²,5'-cycLOURIDINE was obtained from 2',3'-O-isopropylideneuridine, triphenylphosphine (I) and diethyl azodicarboxylate (II). Attempted use of this reaction with unprotected uridine, however, led predominantly to the formation of 2',3'-O-(triphenyl)phosphoranyl-0²,5'-cycLOURIDINE (III) and no 0²,5'-cycLOURIDINE (IV) could be obtained. In this communication, we wish to report the preparation and some reactions of III.

To a suspension of uridine (1.22g, 5 mmol) and three equivalents of I in tetrahydrofuran (THF, 10 ml) was added dropwise three equivalents of II in THF (2 ml) at room temperature with exclusion of moisture and the stirring was continued for 2 hrs. The uridine remaining insoluble disappeared as reaction proceeded and a fine powdered product was precipitated which was proved to be III by following experiments and elemental analysis (1.51g, 62%, recrystallization from DMF, mp. >250°C, $\lambda_{\text{max}}^{\text{MeCN}}$ 232 nm, nmr(DMSO-d⁶) 7.28 (15H PPh) 5.86 (br.s, 1H C₁,H) 4.70, 4.50, 4.23 ppm (5H C₄,H, C₃,H, C₂,H, C₅,H)). On treatment with dil. acetic acid or ammonia, III was readily hydrolyzed to give uridine and triphenylphosphine oxide in a ratio of about 1 : 1. When III in THF-water (1 : 1) was stirred for 3 days at room temperature, IV was obtained in a 70% yield (decomp. ~265°C, $\lambda_{\text{max}}^{\text{MeOH}}$ 238 nm).³ Similar to the case of 2',3'-O-isopropylidene-0²,5'-cycLOURIDINE,⁴ III gave 0²,methyluridine in an 80% yield by refluxing in methanol for 10 hrs (mp. 173°C, $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 253, 229 nm, λ_{min} 238, 213 nm). Similarly, 0²,ethyluridine was isolated in a 41% yield (mp. 176~177°C, $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 253, 228 nm, λ_{min} 237, 213 nm). On treatment with methanol saturated with ammonia (room temperature) at room temperature for 5 days, III quantitatively gave isocytidine which was further converted into 2',3'-O-isopropylideneisocytidine by treatment with 2,2-dimethoxypropane in the presence of p-toluenesulfonic acid. The formation of 2',3'-O-isopropylideneisocytidine shows that no epimerization of 2'- and 3'-hydroxyl group takes place during the methanolysis of phosphorus-oxygen bonds. An additional confirmation of the structure was obtained as follows; when IV was allowed to react with I and II in THF at room temperature,

III was isolated in a 73% yield.



The $0^2,5'$ -anhydro bond of 2',3'-O-isopropylidene- $0^2,5'$ -cyclocytidine was readily cleaved by the reaction with acetyl halides.⁵ Thus III was allowed to react with 1.5 molar amounts of acetyl bromide in THF giving 5'-bromo-5'-deoxycytidine in a 60% yield along with a small amount of unidentified product. The reaction of III with benzoyl bromide afforded N^3 -benzoyl-5'-bromo-5'-deoxycytidine in a 72% yield (softening at 78°C $\lambda_{\text{max}}^{\text{MeOH}}$ 255 nm, λ_{min} 226 nm). This result suggests that the reaction proceeds through an iminium salt (V).



It is noteworthy that alcohols and water initially attack the phosphorus-oxygen bonds of III while the $0^2,5'$ -anhydro bond of III is more readily cleaved by acyl bromides.

Further application of III for the synthesis of uridine derivatives, together with reaction mechanism, is currently under investigation.

References

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