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

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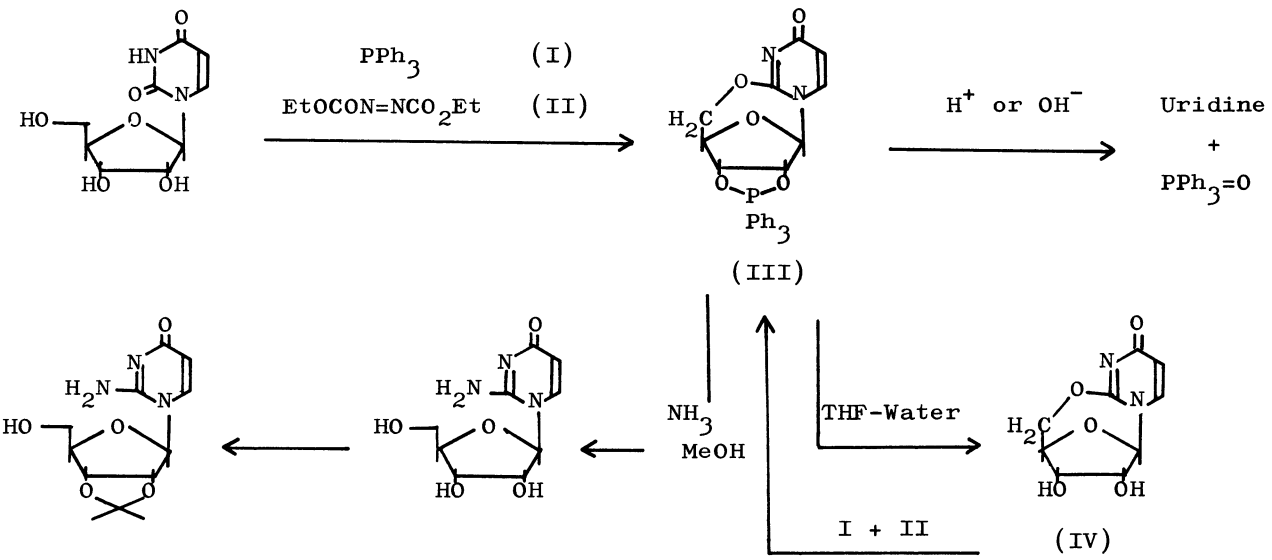
The reaction of uridine, triphenylphosphine (I) and diethyl azodicarboxylate (II) in THF gave 2',3'-O-(triphenyl)phosphoranyl-$O^2$,5'-cyclouridine (III). The alkaline or acid hydrolysis of III gave uridine and triphenylphosphine oxide ( 1 : 1 ). The treatment of III in THF-water afforded $O^2$,5'-cyclouridine.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

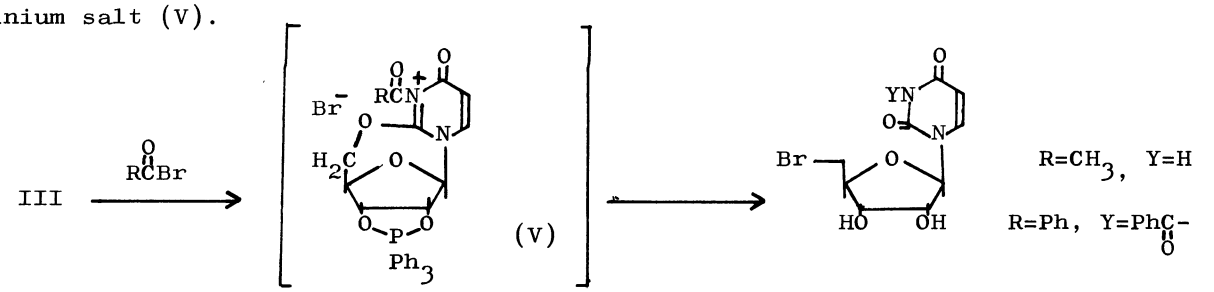
Cyclonucleosides have been used as important intermediates for the synthesis of nucleosides and nucleotides.[1] In a previous paper,[2] we have reported that 2',3'-O-isopropylidene-$O^2$,5'-cyclouridine was obtained from 2',3'-O-isopropylideneuridine, triphenylphosphine (I) and diethyl azodicarboxylate (II). Attempted use of this reaction with unprotected uridine, however, led predominantly to the formation of 2',3'-O-(triphenyl)phosphoranyl-$O^2$,5'-cyclouridine (III) and no $O^2$,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 temprature 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 elmental analysis ( 1.51g, 62%, recrystallization from DMF, mp. $>$ 250°C, $\lambda_{max}^{MeCN}$ 232 nm, nmr(DMSO-$d^6$) 7.28 (15H PPh) 5.86 (br.s,1H $C_1$,H) 4.70, 4.50, 4.23 ppm (5H $C_4$,H,$C_3$,H, $C_2$,H,$C_5$,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 temprature, IV was obtained in a 70% yield ( decomp. ~265°C, $\lambda_{max}^{MeOH}$ 238 nm).[3] Similar to the case of 2',3'-O-isopropylidene-$O^2$,5'-cyclouridine,[4] III gave $O^2$-methyluridine in an 80% yield by refluxing in methanol for 10 hrs (mp. 173°C, $\lambda_{max}^{H_2O}$ 253, 229 nm, $\lambda_{min}$ 238, 213 nm). Similarly, $O^2$-ethyluridine was isolated in a 41% yield (mp. 176~177°C, $\lambda_{max}^{H_2O}$ 253, 228 nm, $\lambda_{min}$ 237, 213 nm). On treatment with methanol saturated with ammonia (room temprature) at room temprature 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 temprature,

III was isolated in a 73% yield.




The $O^2$,5'-anhydro bond of 2',3'-O-isopropylidene-$O^2$,5'-cyclouridine 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'-deoxyuridine 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'-deoxyuridine in a 72% yield (softening at 78°C $\lambda_{max}^{MeOH}$ 255 nm, $\lambda_{min}$ 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 $O^2$,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.

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