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STUDIES ON NUCLEOSIDES AND NUCLEOTIDES. IV. SYNTHESIS AND REACTIONS OF 3',5'-O-(TRIPHENYL)PHOSPHORANYLADENOSINE

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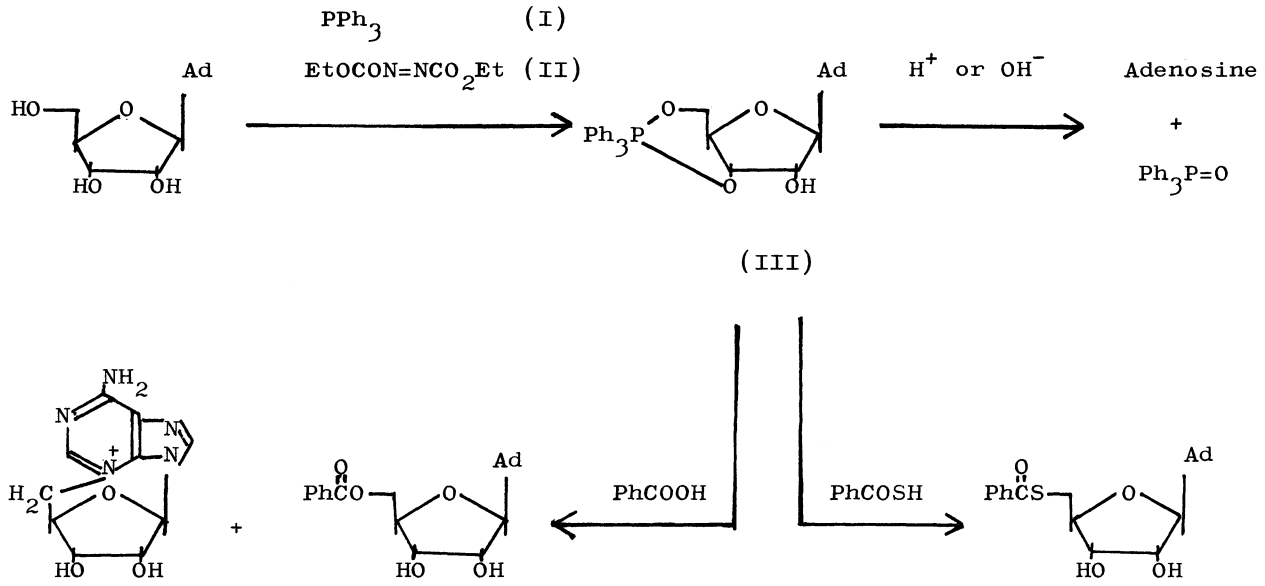
The reaction of adenosine with triphenylphosphine (I) and diethyl azodicarboxylate (II) in dioxane at 70°C gave 3',5'-O-(triphenyl)phosphoranyladenosine (III). This compound was readily hydrolyzed to give adenosine and triphenylphosphine oxide (1 : 1). The reaction of III with benzoic acid in dioxane gave 5'-O-benzoyladenosine and N^3, 5'-cycloadenosine. On treatment with phenyl isocyanate, III gave 5'-O-phenylcarbamoyladenosine and 5'-O-phenylcarbamoyl-N^6-phenylureidoadenosine, and with diphenylketene, III gave 5'-O-diphenylacetyladenosine and N^6,5'-O-bis-diphenylacetyladenosine.

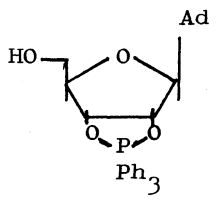
In a previous paper,[1] we have reported that 2',3'-O-(triphenyl)phosphoranyl-O^2, 5 -cyclouridine was obtained from uridine, triphenylphosphine (I) and diethyl azodicarboxylate (II). In this communication, we wish to report the reaction of adenosine with I and II.

To a suspension of adenosine (2.67g, 10 mmol) and 1.5 equivalents of I in dioxane (20 ml) was added dropwise over a period of 3 hr 1.5 equivalents of II in dioxane (10 ml) at 70°C with exclusion of moisture and the temperature was kept at 70°C until adenosine disappeared. The reaction mixture was then allowed to cool to room temperature, whereupon a powdered product separated from the solution. The product was proved to be 3',5'-O-(triphenyl)phosphoranyladenosine (III) by following experiments and elemental analysis (3.95g, 75%, recrystallization from dioxane, mp. 171~172°C, λ_{max}^{MeCN} 260 nm (ε 7400), λ_{min} 245 nm, nmr (DMF-d_7)[2] 7.59 (15H, PPh) 6.01 (d, 1H, C_1,H) 4.84, 4.22, 4.10 ppm (5H, C_2,H, C_3,H, C_4,H, C_5,H)). The hydrolysis of III was readily accomplished by dil. acetic acid or ammonium hydroxide to give adenosine and triphenyl-

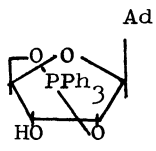
phosphine oxide (1 : 1). On treatment with 3 equivalents of thiobenzoic acid in pyridine at room temperature, III gave 5'-O-thiobenzoyladenosine (40%, recrystallization from MeOH, mp. 159~161°C, $\lambda_{max}^{H_2O}$ 262 nm (ε 13800), 248 nm (ε 11500), λ_{min} 225 nm).[3] When III was allowed to react with 3 equivalents of benzoic acid in dioxane at 70°C, 5'-O-benzoyladenosine (59%, recrystallization from MeCN, mp. 163~165°C, $\lambda_{max}^{H_2O}$ 260 nm (ε 11000), 238 nm (ε 12000), λ_{min} 252, 224 nm)[3] and N^3,5'-cycloadenosine (16%, $\lambda_{max}^{H_2O}$ 273 nm, λ_{min} 229 nm)[4] were formed. These results indicated that the structure of the



phosphorus containing compound should be III. Alternative structures, III' and III'', were ruled out by the chemical evidence mentioned above and by the examination of molecular model, respectively.



(III')

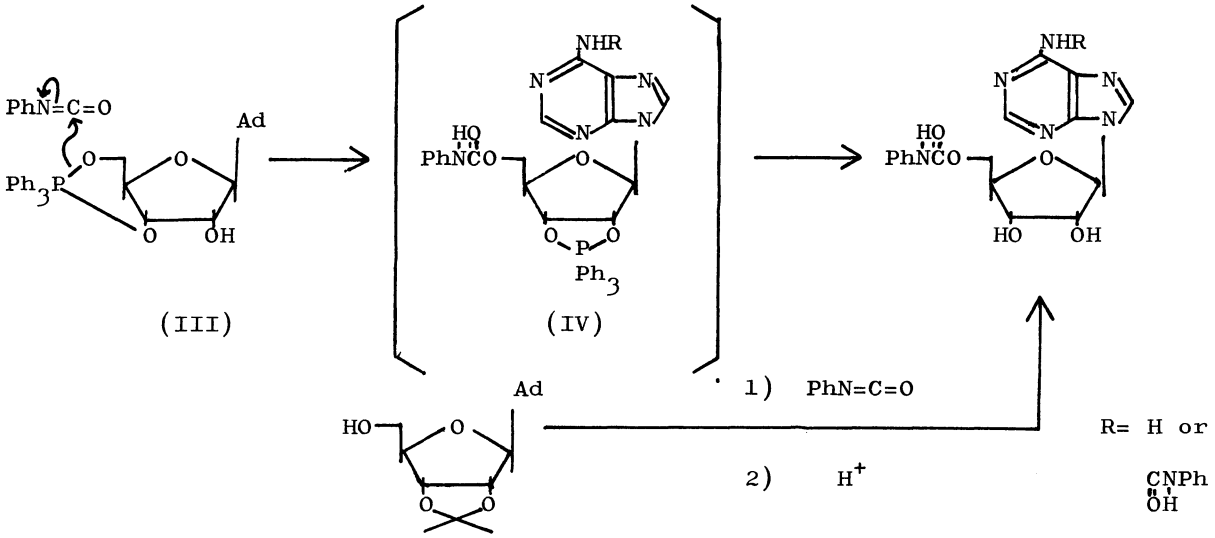


(III'')

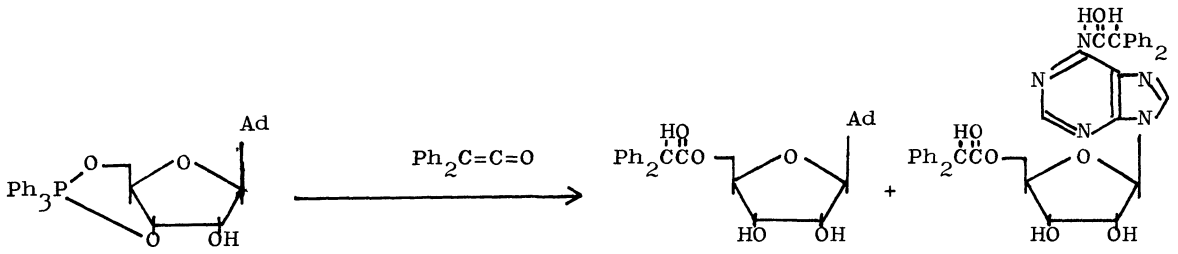
Since III is readily hydrolyzed to adenosine, the III seemed to be an attractive intermediate for the protection of 2'-hydroxyl group of adenosine. Thus, several attempts were made to introduce tetrahydropyranyl and acyl groups to that position. However, many side products were formed and no expected products could be isolated.

Next, the reaction of III with phenyl isocyanate was attempted. When III was

allowed to react with 3 equivalents of phenyl isocyanate in pyridine at room temperature for 1 day, 5'-O-phenylcarbamoyladenosine (34%, recrystallization from MeOH, mp. 181~183°C, $\lambda_{max}^{H_2O}$ 262 nm (ε 12100), 238 nm (ε 17100), λ_{min} 253, 223 nm) and 5'-O-phenylcarbamoyl-N^6-phenylureidoadenosine (45%, recrystallization from MeOH, softening at 145°C, λ_{max}^{MeOH} 280 nm (ε 29900), 235 nm (ε 27200), λ_{min} 253, 225 nm)[3,5] were isolated by preparative tlc and no 2 - and/or 3'-O-phenylcarbamoyladenosine were obtained. The structures of the products were established by the unambiguous synthesis from 2',3'-O-isopropylideneadenosine and phenyl isocyanate followed by acid hydrolysis. The unexpected formation of 5'-O-phenylcarbamoyladenosine would be explained by assuming that phenyl isocyanate reacts more readily with 3',5'-O-phosphoranyl bond than



with the 2'-hydroxyl group of III. This result suggested that the intermediate might be 5'-O-phenylcarbamoyl-2',3'-O-(triphenyl)phosphoranyladenosine (IV) which was hydrolyzed to 5'-O-phenylcarbamoyladenosine during working up. That IV is less reactive than III was supported by the following fact. When 5'-O-phenylcarbamoyl-N^6-phenylureidoadenosine was reacted with I and II in THF, followed by treatment with 10 molar equivalents of phenyl isocyanate in pyridine, the starting material was recovered in a 53% yield. Similar to the case of phenyl isocyanate, III reacted with 3 equivalents of diphenylketene to give 5'-O-diphenylacetyladenosine (21%, recrystallization from MeCN, softening at 180°C, λ_{max}^{MeOH} 260 nm (ε 12600), λ_{min} 235 nm) and N^6,5'-O-bis-diphenylacetyladenosine (46%, recrystallization from benzene-ether, softening at 95°C, λ_{max}^{MeOH} 278 nm (ε 17500), λ_{min} 240 nm).[3] These products were hydrolyzed by treatment with saturated ammonia in methanol for 8 hr to give adenosine.



(III)

The work described in this paper demonstrates that the reaction of adenosine with I and II gave III in a good yield. Further applications of III for the synthesis of adenosine derivatives are currently under investigation.

References

1) J.Kimura, Y.Fujisawa, T Sawada and O Mitsunobu, Chem. Lett., 691 (1974).

2) Ultraviolet spectra were taken with a Hitachi spectrophotometer EPS-3T. Nmr spectra were measured with a Hitachi-Perkin-Elmer R-20 spectrometer (60 MHz) using TMS as internal reference.

3) The nmr, ir and elemental analysis were consistent with the structural assignment.

4) The yield was calculated by paper chromatographical analysis.

5) Agarwal and Khorana reported that 3',5'-bis-O-(phenylcarbamoyl)-N^6-phenylureido-deoxyadenosine had λ_{max}^{EtOH} 278 nm.
K.L.Agarwal and H.G Khorana, J. Amer. Chem. Soc., 94, 3578 (1972).

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