A Direct Synthetic Method of Nucleotides

Sir:

The recent communication\(^1\) from our laboratory has reported a convenient synthetic method for natural and unnatural nucleotides by fusing silyl derivatives of purine or pyrimidine with phosphorylated halogeno sugars. The communication of Leonard and Laursen\(^2\), which deals with the synthesis of 3-β-d-ribofuranosyladenine and adenosine, starting from protected halogeno sugars prompted us to investigate a direct (one step) synthetic method by which we synthesized several purine nucleotides and uridylic acid.

When 6-benzamido purine (I) was allowed to react with 1-bromo 2, 3-di-O-benzoyl-5-diphenyl-phosphoryl-d-ribofuranose\(^3\) (II) in dimethylformamide at 40–50°C for 40 hr., 9-(2',3'-di-O-benzoyl-5'-diphenyl-phosphoryl-d-ribofuranosyl) benzamidopurine (III) was obtained in 67% yield, whereas no 3-substituted adenine could be detected. The same result was obtained by using nitromethane, dimethyl sulfoxide, acetonitrile and dimethylacetamide as solvents instead of dimethylformamide. In each instance, the proceeding of the reaction was determined by thin layer chromatography.

After removal of one phenyl and two benzoyl groups by alkaline hydrolysis and the subsequent removal of the remaining phenyl group attached to phosphoryl residue with phosphodiesterase prepared from Trimeresurus flavoviridis (Hallowell), III was converted into 5'-adenylic acid (5'-AMP) (V). V was identical with authentic sample of 5'-adenylic acid in its physical properties and paper chromatographic behavior.

On the other hand, when adenine (VI) was allowed to react with 1-bromo-2, 3-di-O-benzoyl-5'-diphenyl-phosphoryl-d-ribofuranose (II) in acetonitrile at 40°C for 40 hr., 9-(2',3'-di-O-benzoyl-5'-diphenyl-phosphoryl-d-ribofuranosyl) adenine (VIII) and the corresponding 3-derivative (VII) were obtained in 23% and 29% yields respectively, but the 1-substituted ade-

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TABLE I. PHYSICAL PROPERTIES AND YIELDS OF THE INTERMEDIATES OF THE SYNTHETIC NUCLEOTIDES

| Compound | M.p.* | ($
 \alpha$)D | Starting base | Solvent | Yield** |
<table>
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<tr>
<td>6-Benzamido-9-(2',3'-di-O-benzoyl-5'-diphenylphosphoryl-D-ribofuranosyl)-purine</td>
<td>amorph.</td>
<td>-48</td>
<td>6-Benzamido-purine</td>
<td>HCON(CH$_3$)$_2$</td>
<td>67</td>
</tr>
<tr>
<td>9-(2', 3'-Di-O-benzoyl-5'-diphenyl-phosphoryl-D-ribofuranosyl)-adenine</td>
<td>147°</td>
<td>-69</td>
<td>Adenine</td>
<td>CH$_3$NO$_2$</td>
<td>31</td>
</tr>
<tr>
<td>3-(2',3'-Di-O-benzoyl-5'-diphenyl-phosphoryl-D-ribofuranosyl)-adenine</td>
<td>160°</td>
<td>-52</td>
<td>Adenine</td>
<td>CH$_3$CN</td>
<td>31</td>
</tr>
<tr>
<td>9-(2',3'-Di-O-benzoyl-5'-diphenyl-***phosphoryl-D-ribofuranosyl)-hypoxanthine</td>
<td>amorph.</td>
<td>-50</td>
<td>Hypoxanthine</td>
<td>HCON(CH$_3$)$_2$</td>
<td>78</td>
</tr>
<tr>
<td>7-(2',3'-Di-O-benzoyl-5'-diphenyl-phosphoryl-D-ribofuranosyl)-theophylline</td>
<td>156°</td>
<td>-26</td>
<td>Theophylline</td>
<td>CH$_3$CN</td>
<td>77</td>
</tr>
<tr>
<td>1-(2',3'-Di-O-benzoyl-5'-diphenyl-phosphoryl-D-ribofuranosyl)-uracil</td>
<td>amorph.</td>
<td>-53</td>
<td>4-Ethoxy-2-pyrimidinone</td>
<td>CH$_3$CN</td>
<td>42</td>
</tr>
<tr>
<td>3-(2',3'-Di-O-benzoyl-5'-diphenyl-phosphoryl-D-ribofuranosyl)-uracil</td>
<td>amorph.</td>
<td>+17</td>
<td>4-Ethoxy-2pyrimidinone</td>
<td>CH$_3$CN</td>
<td>42</td>
</tr>
</tbody>
</table>

* Melting points are uncorrected.
** Yields of the intermediates based on the reacted bases.
*** An unknown nucleoside derivative was also produced as a minor component.

nine could not be detected.

In this case also, the above-mentioned solvents were effective for the reaction.

After removal of the protecting groups by the method mentioned above, VII and VIII were converted into the corresponding 3-β-D-ribofuranosyladenine-5'-phosphoric acid (V') (m.p. 205°C (decomp.), Anal. Found: C, 33.68; H, 4.54; N, 18.95; P. 8.17%) and 5'-adenylic acid (5'-AMP), respectively. The latter compound was identical with the authentic sample of adenylic acid by the similar method mentioned above.

Characterization of V' as 3-substituted adenine was readily achieved by the ultraviolet absorption spectra in neutral H$_2$O ($\lambda_{max}$ 274.5 m$\mu$
(11,809); $\lambda_{\text{min}}^{\text{pH} 7.0}$ 245.5 m$\mu$) and acid media
($\lambda_{\text{max}}^{\text{pH} 1.0}$ 274.5 m$\mu$ (16,000); $\lambda_{\text{min}}^{\text{pH} 1.0}$ 237.5 m$\mu$,
($\lambda_{\text{min}}$ at pH 1.0)–($\lambda_{\text{min}}$ at pH 7.0) = –8 m$\mu$).
Furthermore, $V'$ was treated with 5'-nucleo-
tidase of snake venom as in the case of $V$ to
give the nucleoside (IX), m.p 210°C (decomp.),
which was identical with the authentic sample
of “3-isoadenosine” in its physical proper-
ties. From the result of nuclear magnetic
resonance analysis ($J_{1',2'} = 1.0$ c.p.s.), it was
also shown that $V'$ possessed $\beta$-configuration
in the glycosidic center. The scope of
reaction was investigated on hypoxanthine,
theophylline and 4-ethoxypyrimidinone-(2)
with phosphorylribofuranosyl bromide deriva-
tive. The results are shown in Table. I.

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