POLYAMINO SUGARS IV. A SYNTHESIS OF A NEW TYPE OF NUCLEOSIDES: METHYL 4,6- \underline{O} -BENZYLIDENE-2,3-DIDEOXY-3-NITRO-2-(7'-THEOPHYLLINYL)- β -D-GLUCOPYRANOSIDE AND ITS 2-(2',6'-DICHLORO-9'-PURINYL) HOMOLOG.

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All naturally occurring nucleosides found up to now have the structure that a nitrogenous heterocyclic base is attached to the anomeric carbon atom of the sugar moiety. Some "cyclonucleosides" have been also described¹⁾, i.e. those having such a structure that the base combines with the sugar moiety both anomerically and otherwise. Recently $Carbon^{2}$ synthesized 3-(6'-amino-9'-puriny1)-2,3-dideoxy-D-erythro-pentose and its D-threo isomer.

In extension of our studies on aminations of nitro sugars³⁻⁵⁾ we have found that some of purine bases can be introduced, with surprising ease, in the C-2 position of 3-nitroglucoside to afford a new type of nucleosides.



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A mixture of methyl 2-Q-acetyl-4,6-Q-benzylidene-3-deoxy-3-nitro- β -D-glucopyranoside(1)⁶⁾(1.41 g, 4.0 mmole) and theophylline(anhyd., 0.72 g, 4.0 mmole) in abs. THF(70 ml) was refluxed in the presence of sodium bicarbonate(0.34 g, 4.0 mmole). After 40 h a spot of 1 on t.l.c.(Rf 0.72)⁷⁾ was disappeared. Then, the undissolved material was filtered off, the filtrate evaporated in vacuo at 40°, and the remained material recrystallized from THF/ethanol to afford in 96% yield methyl 4,6-Q-benzylidene-2,3-dideoxy-3-nitro-2-(7'-theophyllinyl)- β -Dglucopyranoside(3), C₂₁H₂₃N₅O₈⁸⁾, m.p. 260-263°(dec., browning above ca. 200°); [α]²⁰_D +51.4°(c 1.00, THF); λ_{max}^{THF} 278.0 mµ (ϵ 6980); Rf 0.20⁷).

Similarly, $\underline{1}$ was allowed to react with a molar equivalent of 2,6-dichloropurine under reflux for 54 h in abs. THF to form methyl 4,6-<u>O</u>-benzylidene-2-(2',6'-dichloro-9'-purinyl)-2,3-dideoxy-3-nitro- β -D-glucopyranoside($\underline{4}$), C₁₉H₁₇-N₅O₆Cl₂⁸, which was twice recrystallized from ethanol/water: Yield 78 %; m.p. 202-204°(dec., browning above ca. 180°); $[\alpha]_D^{2O}$ +27.9°(<u>c</u> 1.00, MeOH); λ_{max}^{MeOH} 273.5 mµ(ϵ 7880); Rf 0.31⁷).

The 3-nitro-hex-2-enoside $\underline{2}$, which is easily prepared from $\underline{1}$ by refluxing in benzene with sodium bicarbonate⁶⁾, reacts also with theophylline in abs. THF at room temperature, slowly without a basic catalyst but rapidly in the presence of a trace of triethylamine, to yield $\underline{3}$ over 80% yields. Therefore, the formation of $\underline{3}$ and $\underline{4}$ from $\underline{1}$ seems to comprise two steps, i.e. (i) the Schmidt-Rutz elimination of acetic acid from $\underline{1}$ to give the nitroolefin $\underline{2}$ and (ii) the Michael addition of the nucleophilic purine bases to $\underline{2}^{4,5,9}$.

A large value of the coupling constants (≥ 7.5 Hz) of the ring protons H¹-H⁵ indicates the β -gluco structure of <u>3</u> and <u>4</u>(cf. Fig. 1 and 2). The point of attachment of the sugar moiety to the purine rings was decided to be the <u>N</u>⁷ position in <u>3</u> and the <u>N</u>⁹ position in <u>4</u> on the basis of the UV spectrometric evidence¹⁰⁴²) as described above.

In the similar fashion, $\underline{1}$ reacts with a molar equivalent of \underline{N}^6 -benzyladenine, but with 1/2 molar equivalent of uracil. Investigations on the fine structures of their products are now in progress.



100 MHz NMR spectra of methyl 4,6-<u>O</u>-benzylidene-2,3-dideoxy-3-nitro-2-(7'-theophyllinyl)- β -D-glucopyranoside(<u>3</u>)[Fig.1]* and its 2-(2',6'-dichloro-9'-purinyl) homolog(<u>4</u>)[Fig.2] in CDCl₃ with a TMS internal standard.

* The ring protons H^1-H^4 were assigned by a double resonance technique.

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- 11. Cf. λ^{THF}_{max} 277 mµ(ε 8700) for 7-(4',6'-<u>O</u>-benzyldene-3'-deoxy-3'-nitro-β-D-glucopyranosyl)-theophylline and λ^{THF}_{max} 277.5mµ(ε 9400) for its 2'-<u>O</u>-acetate [T. Nakagawa and T. Takamoto, unpublished results].
- 12. Cf. λ^{MeOH}_{max} 274 mµ(ε 9410) for 9-(2'-acetamido-3',5',6'-tri-<u>O</u>-acetyl-2'-deoxy-D-glucofuranosyl)-2,6-dichloropurine[M. L. Wolfrom and M. W. Winkley, <u>J. Org. Chem.</u>, <u>31</u>, 3711(1966) and λ^{EtOH}_{max} 273 mµ(ε 8900) for 2,6-dichloro-9-(2',3',4',6'-tetra-<u>O</u>-acetyl-β-D-glucopyranosyl)-purine[Y. Ishido, T. Ma-tsuba, A. Hosono, K. Fujii and T. Sato, <u>Bull. Chem. Soc. Japan</u>, <u>40</u>, 1007 (1967)].