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## Recovery of useful carbohydrates in nucleoside syntheses: 2,5-di-*O*-benzoyl-3-deoxy-β-D-*erythro*-pentofuranose*

The mercury derivative of 2-acetamido-6-chloropurine[1] was first employed in nucleoside synthesis for the preparation of the anomers of 2′-deoxy-6-thioguanosine and related compounds. The method has been extended[2] to the preparation of 3′-deoxy-6-thioguanosine, L-thioguanosine, and some related nucleosides. The proposed[2] generality of this synthetic route and the interesting biological properties attributed to various nucleosides derived from thioguanine[3], which necessitates their preparation in amounts sufficient for chemotherapeutic evaluation, prompt us to record our further observations on this synthetic method.

In previous work[4] on the synthesis of moderately large quantities of the anomers of 2′-deoxy-6-thioguanosine[1], we have examined the coupling mixture after removal of the nucleosides and the unreacted purine starting-materials, and have found the protected, (1→1)-linked, disaccharide of 2-deoxy-D-*erythro*-pentofuranose to be a major artifact in this reaction. This compound has proved valuable from a practical standpoint in that it is readily reconvertible into a glycosyl halide that could be re-used in the nucleoside synthesis, thus decreasing the cost and effort necessary to prepare quantities of these compounds sufficient for biological evaluation. The formation of the disaccharide was attributed to the presence, or generation, of water during the nucleoside synthesis or to the formation of a labile purine–mercury–sugar complex, which was decomposed during the isolation and purification process. The exact nature of this mechanism has remained in doubt largely because of the obscure nature of the mercury complex of 2-acetamido-6-chloropurine[1], wherein the elements Hg and $O_2$ are added to give a complex of unknown structure. In the preparation of 2-acetamido-6-chloro-9-(2,5-di-*O*-benzoyl-3-deoxy-β-D-*erythro*-pentofuranosyl)-9*H*-purine[2] by the coupling of the mercury complex of 2-acetamido-6-chloropurine and 2,5-di-*O*-benzoyl-3-deoxy-β-D-*erythro*-pentofuranosyl chloride[2], it was found[2] that the addition of molecular sieves** is useful. It has further been observed that the mode of addition of the molecular sieves is important. The overall yield in the coupling is materially increased when the azeotropically dried mercury

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**Linde, Type 4A, 1/16″ pellets.

complex is first treated with a portion of the sieves in refluxing xylene, and the glycosyl halide and the remainder of the sieves are then added. The residues from the reaction mixture, after removal of the coupling product and the unreacted purine starting-material, yielded a syrup that showed a prominent hydroxyl band in its i.r. spectrum, in contrast to the 2-deoxy-D-*erythro*-pentofuranosyl derivatives, which show no such absorption. Chromatography of the crude syrup on neutral alumina yielded a main, crystalline component whose microanalysis and molecular weight were in agreement for that of a di-*O*-benzoyl-deoxy-pentose. The n.m.r. spectrum indicated that the material was mainly the β-D anomer (singlet for H-1′) contaminated with a trace of what was presumed to be the α-D anomer (doublet for H-1′). Recrystallization from methanol–water afforded the pure β-D anomer in approximately 10% yield from the crude syrup. For recycling, it was not necessary to go through the wasteful process of isolation; instead, the crude syrup was treated with acetyl chloride–hydrogen chloride as in the preparation of the glycosyl chloride[2] from methyl 2,5-di-*O*-benzoyl-3-deoxy-β-D-*erythro*-pentofuranose[5]. The crude, syrupy chloride thus obtained was coupled with an equivalent of the 2-acetamido-6-chloropurine–mercury complex to give an additional 21% of 2-acetamido-6-chloro-9-(2,5-di-*O*-benzoyl-3-deoxy β-D-*erythro*-pentofuranosyl)-9*H*-purine for an overall yield of 52%, as compared with a literature[2] yield of 24% *with* isolation of the intermediate chloride. The experience in these two nucleoside series would indicate that the neutral portion of the nucleoside coupling-mixture may constitute a rich source of re-usable sugar derivatives. Rather low yields (20–50%) are commonly realized in coupling reactions, and it would appear that the bulk of the material is usually lost or discarded in processing the reaction mixture. Despite the supposedly sensitive nature often attributed to the glycosyl halides, it would appear that, actually, they are rather stable under the reaction conditions, and often undergo but little decomposition during the nucleoside synthesis. It may, therefore, prove useful to examine routinely nucleoside coupling-mixtures with a view toward recovery of re-usable carbohydrate intermediates.

## EXPERIMENTAL

*2-Acetamido-6-chloro-9-(2,5-di-*O*-benzoyl-3-deoxy-β-*D*-*erythro*-pentofuranosyl)-9H-purine*[2]. — The mercury complex of 2-acetamido-6-chloropurine[1] (235 mmoles) on Celite was suspended in dry xylene (6 liters), and a portion of the solvent (~ 800 ml) was distilled off, so as to dry the mixture. Molecular sieves (Linde, Type 4A, 1/16″ pellets, 80 g) were added, and the mixture was stirred for 3–5 min under reflux. The crude glycosyl chloride[2], prepared from methyl 2,5-di-*O*-benzoyl-3-deoxy-β-D-*erythro*-pentofuranose[5] (85.6 g, 235 mmoles), and a second portion of molecular sieves (80 g) were then added. The mixture was stirred for 6 h under reflux, and then filtered hot, and the filtrate was diluted with petroleum ether (b.p. 30–60°, 12 liters). The filter cake was washed with chloroform, and the washings (*A*) were preserved. 2-Acetamido-6-chloropurine could be recovered from the cake as previously described[4]. The material precipitated by petroleum ether was recovered by filtration, and dissolved in the chloroform washings (*A*). The solution of the crude,

protected nucleoside was extracted twice with 30% aqueous potassium iodide (to free it from mercury), and the organic layer was washed with water and dried (magnesium sulfate). The filtrate was evaporated to dryness *in vacuo*, and the residue was triturated with a small volume of benzene to yield crystals (38.7 g, 31%); m.p. 195–198°, $[\alpha]_D^{24.5}$ +25.5° (*c* 0.5, chloroform) {lit.[2] m.p. 197.5–203.5°, $[\alpha]_D^{23}$ +24° (*c* 0.5, chloroform)}. The u.v. spectral data were in good accord with the literature[2] values.

*Recovery of 2,5-di-O-benzoyl-3-deoxy-β-D-erythro-pentofuranose.* — The combined, petroleum ether filtrates from the coupling of 176 g of crude glycosyl chloride were evaporated *in vacuo* to a syrup which was dissolved in chloroform, and freed of mercury by extraction with 30% aqueous potassium iodide. The organic layer was washed with water, dried (magnesium sulfate), and evaporated to dryness *in vacuo* to a heavy syrup (127.5 g). A portion of this syrup (10 g) was dissolved in the minimal volume of benzene, and the solution was applied to a column of Woelm neutral alumina (activity I, 300 g). Elution with benzene and ethyl acetate–benzene yielded syrups until 1:1 benzene–ethyl acetate was reached, whereupon material began to be eluted that crystallized. Continued elution, first with 1:10 chloroform–ethyl acetate, and then with chloroform, yielded a total of 3.8 g of crude, crystalline solid. Recrystallization from methanol–water (carbon) gave colorless crystals; m.p. 89–91°. The elementary analysis, molecular-weight determination, and n.m.r. spectrum indicated that this was essentially pure 3,5-di-*O*-benzoyl-3-deoxy-β-D-*erythro*-pentofuranose containing a trace of what was presumed to be the α-D anomer, as evidenced by the n.m.r. spectrum (doublet, $\delta$ 5.87, $J_{1',2'}$ 3.4 Hz). The material was recrystallized once more, yielding the pure β-D anomer (1.0 g); m.p. 89–91°, $[\alpha]_D^{22.5}$ +23.8° (*c* 1.0, chloroform); n.m.r. data (chloroform-*d*, tetramethylsilane as internal standard, Varian A-60A spectrometer): $\delta$ 8.1, 7.5 (10-proton multiplet, aromatic), $\delta$ 5.58 (1-proton singlet, H-1), $\delta$ 5.45, 5.35 (1-proton pair of doublets, H-2, *J* 2.5 Hz), $\delta$ 4.5 (3-proton multiplet, H-4, H-5), $\delta$ 4.1 (one-proton, broad singlet, exchanges, OH), $\delta$ 2.3 (2-proton multiplet, H-3). The compound moved as a single spot on t.l.c. (silica gel–chloroform).

*Anal.* Calc. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30; O, 28.04. Found: C, 66.64; H, 5.39; O, 27.86.

A portion of the syrup recovered from the petroleum ether solution (177 g) was dissolved in acetic acid (400 ml) and treated by the literature[2] procedure for preparation of the glycosyl chloride. The crude chloride was coupled with 2-acetamido-6-chloropurine–mercury complex (125.7 g, 285 mmoles), and processed as already described, to give the protected nucleoside (32.6 g, 21.5%), m.p. 197.5–200°, having spectral and chromatographic behavior identical with that of the sample already prepared.

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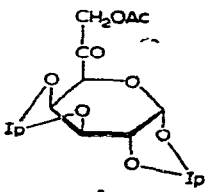
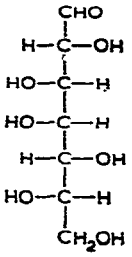
## Un nouvel heptose, le L-*glycéro*-D-*galacto*-heptose

Nous avons décrit récemment[1] la synthèse commode d'un heptulose protégé, le 7-*O*-acétyl-1,2:3,4-di-*O*-isopropylidène-α-D-*galacto*-heptos-6-ulose (**1**) par allongement à l'extrémité non réductrice du D-galactose. Nous avons obtenu, avec un rendement final de 43%, une huile recristallisable dans l'éther isopropylique par réduction d'une solution éthérée de **1** par $LiAlH_4$. Ce traitement doit transformer la partie acétate α-cétonique de la molécule en α-diol. Les cristaux obtenus paraissent homogènes, mais n'ont pas pu être obtenus avec la composition attendue. Après une hydrolyse acide, nous n'avons pu isoler qu'un seul produit cristallisé, dont toutes les propriétés examinées sont celles de l'heptose énantiomorphe **2** du D-*glycéro*-L-*galacto*-heptose déjà connu[2] (Tableau I). Le rendement est de 24% à partir de l'heptulose protégé **1**. Par réduction de l'heptose avec $NaBH_4$, on retrouve le L-*glycéro*-D-*galacto*-heptitol, polyol déjà préparé par une voie différente[3] (Tableau II).




1




2

Le L-*glycéro*-D-*galacto*-heptose cristallise facilement à partir du méthanol, mais nous n'avons pas de preuves sur la structure cyclique de ces cristaux. Il est raisonnable d'admettre que c'est un dérivé sur C-6 du D-galactopyranose *C 1*, la chaîne $CHOH\text{-}CH_2OH$ adoptant la position équatoriale. La mutarotation monotone décroissante suggère une anomérisation α→β. Ceci pourrait être confirmé par