products was obtained as indicated by a chromatographic examination.

The results so far suggest that primary hydroxyl groups and amino groups of partially protected sugars react with sugar isothiocyanates in the anticipated way without difficulty. With secondary hydroxyl groups, however, no such reaction occurs to any appreciable extent. The work on this type of reaction and on an application of the method to polysaccharides is being continued.

Experimental Section

Specific rotations were determined in semimicropolarimeter tubes with lengths of 2 or 1 dm, with a Zeiss polarimeter having a scale reading to 0.01°. Infrared spectra were determined on a Nihon-Bunko spectrophotometer, Model IR-S, using a KBr pellet. The silicic acid used for chromatography was "Silicagel Kanto" from Kanto Kagaku Co., Tokyo (100–200 mesh), without pretreatment. The eluents were used in the following sequence individually or in binary mixtures: benzene, ether, ethyl acetate, acetone, and methyl alcohol. The silica gel used for thin layer chromatography was Wakogel B-O from Wako Chemical Co., Tokyo, activated at 110°. Evaporations were done *in vacuo* at 35–40° (bath temperature). The microanalyses were carried out by the member of the Central Analysis Room, Faculty of Pharmaceutical Sciences, University of Tokyo.

6-*O*-[*N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)thiocarbamyl]-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (IV).—To a solution of 0.70 g of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (II) in 10 ml of dry pyridine was added 1.0 g of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (I), and the solution was kept at 55° for 48 hr. The reaction mixture was concentrated to a syrup; the syrup was freed from pyridine by codistillation with toluene, diluted with a small amount of ethyl alcohol, and left at room temperature. The white needles deposited were recrystallized from ethyl alcohol to give 0.13 g of 1,3-bis(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiourea (VI): mp 209–210°; $[\alpha]^{20}D$ −2.3° (*c* 1.30, chloroform); λ_{max}^{KBr} 2.98 (NH), 5.71 (OAc), 6.13, and 6.54 μ (NHCS).

Anal. Calcd for $C_{29}H_{40}N_2O_{18}S$: C, 47.28; H, 5.47; N, 3.80. Found: C, 47.44; H, 5.36; N, 3.62.

The filtrate was concentrated and the residue was dissolved in benzene and chromatographed on silica gel. After elution with a mixture of benzene–ether (4:1) and reprecipitation from chloroform and hexane, 0.70 g (42%) of IV was obtained as an amorphous powder. The purity of the product was examined by thin layer chromatography using pyridine–*n*-butyl alcohol–water (15:70:15, v/v) and 5% methyl alcohol in benzene as developing solvents and anisaldehyde–sulfuric acid[7] to detect the spots. In each case, one spot developed with R_f 0.91 and 1.58, respectively (with f being 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose); $[\alpha]^{20}D$ −34.2° (*c* 0.79, chloroform); λ_{max}^{KBr} 3.06 (NH), 5.71 (OAc), 6.13, 6.58 (NHCS), and 8.50 μ (isopropylidene).

Anal. Calcd for $C_{27}H_{39}NO_{15}S$: C, 49.92; H, 6.05; N, 2.15; mol wt, 650. Found: C, 50.57; H, 6.12; N, 2.17; mol wt (Rast), 650.

1,2,3,4-Tetra-*O*-acetyl-6-*O*-[*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiocarbamyl]-β-D-glucopyranose (V).—An amount of 0.90 g of 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose (III) in 15 ml of dry pyridine was condensed with 1.0 g of I; the reaction products were separated as described above. Elution of the silica gel column with benzene–ether (4:1, v/v) produced, after evaporation of the solvent and recrystallization from a mixture of chloroform and ether, 0.23 g of the starting material III. Benzene–ether (3:2, v/v) eluted a fraction which, after recrystallization from ethyl alcohol, gave 0.50 g (27%) of V as white needles: mp 167–169°; $[\alpha]^{25}D$ +24.4° (*c* 0.78, chloroform); λ_{max}^{KBr} 3.00 (NH), 5.71 (OAc), 6.13, and 6.54 μ (NHCS).

Anal. Calcd for $C_{29}H_{39}NO_{19}S$: C, 47.21; H, 5.33; N, 1.90. Found: C, 47.27; H, 5.44; N, 2.13.

Further elution of the column with the same solvent gave 0.20 g of crystalline material, mp 207–209°, identical with VI by mixture melting point.

(7) E. Stahl and U. Kaltenbach, *J. Chromatog.*, **5**, 351 (1961).

1,2,4,6-Tetra-*O*-acetyl-2-[2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylthioureido]-2-deoxy-β-D-glucopyranose (VIII).—A portion of 1.0 g of I was added to a solution of 0.90 g of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose (VII) in 15 ml of dry pyridine; the mixture was kept at 55° for 48 hr, then concentrated to dryness, and the remaining pyridine was removed by codistillation with toluene. The residue was recrystallized twice from ethyl alcohol to give 1.10 g (58%) of VIII in the form of white needles: mp 178°; $[\alpha]^{20}D$ +4.9° (*c* 1.72, chloroform); λ_{max}^{KBr} 2.96 (NH), 5.71 (OAc), 6.13, and 6.50 μ (NHCS).

Anal. Calcd for $C_{29}H_{40}N_2O_{18}S$: C, 47.28; H, 5.47; N, 3.80. Found: C, 46.91; H, 5.65; N, 3.82.

Acknowledgment.—The author wishes to thank Professor S. Akiya for his interest in this work.

The Formation of 1,1′-(2-Deoxy-D-ribofuranosyl-2′-deoxy-D-ribofuranoside) Tetra-O-*p*-toluate in the Synthesis of 2-Deoxy-D-ribofuranosyl Nucleosides[1]

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Received April 21, 1966

In the course of preparing moderately large-scale quantities of the α and β anomers of 2′-deoxythioguanosine[2] by the coupling of the mercury complex of 2-acetamido-6-chloropurine[2] and 2-deoxy-α-D-ribofuranosyl chloride,[3] we have had occasion to examine the coupling mixture after removal of the nucleosides and unreacted purine starting materials. The resulting residue after evaporation of solvents was a partially crystalline syrup whose infrared spectrum indicated the absence of hydroxyl absorption and was quite similar to that of the methyl glycoside of 2-deoxy-D-ribofuranose 3,5-di-O-*p*-toluate. Crystallization of the crude syrup from methanol gave a well-defined chromatographically pure solid in poor yield, mp 149–150°, $[\alpha]^{23.8}D$ −15° ($CHCl_3$), whose elementary analysis was in accord with the empirical formula $C_{42}H_{42}O_{11}$ indicating a composition for the product as one composed of two di-*p*-toluoyl-2-deoxyribosyl segments plus an atom of oxygen. An osmometric molecular weight determination also favored a "dimeric" formula of this type. The crystalline material on solution in glacial acetic acid and treatment with anhydrous hydrogen chloride gave a good yield of 2-deoxy-α-D-ribofuranosyl chloride 3,5-di-O-*p*-toluate with melting point, optical rotation, and infrared spectrum identical with that of a sample prepared in the same manner from 1-O-methyl-2-deoxy-D-ribofuranose 3,5-di-O-*p*-toluate.[3] For recovery of the rather expensive halo sugar, it has

(1) (a) 1,1′-(2-Deoxy-D-*erythro*-pentofuranosyl-2′-deoxy-D-*erythro*-pentafuranoside) tetra-O-*p*-toluate. (b) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-3764. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center.

(2) R. H. Iwamoto, E. M. Acton, and L. Goodman, *J. Med. Chem.*, **6**, 684 (1963).

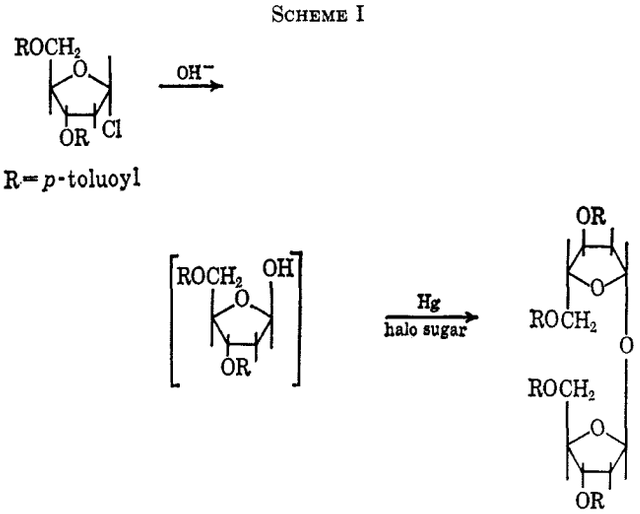
(3) M. Hoffer, *Chem. Ber.*, **93**, 2777 (1960); M. Hoffer, R. Duschinsky, J. J. Fox, and N. Yung, *J. Am. Chem. Soc.*, **81**, 4112 (1959); A. K. Bhattacharya, R. K. Ness, and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 428 (1963).

not been necessary to resort to the wasteful crystallization of the intermediate, but instead, the entire syrupy residue after removal of the nucleosides and starting purine was treated with dry hydrogen chloride in acetic acid solution resulting in the reclamation of 25–30% of the initial weight of blocked 2-deoxy-α-D-ribofuranosyl chloride in a state of purity suitable for reuse in the nucleoside synthesis. The nmr spectrum of the crystalline product gives a total integration of 21 protons and was quite similar to the published spectrum of 1-O-methyl-2-deoxy-D-ribofuranose 3,5-di-O-*p*-toluate[4] lacking the band assigned to O-methyl.

The available evidence would most easily accommodate a structure for the dimeric product as being that of 1,1′-(2-deoxy-D-ribofuranosyl-2′-deoxy-D-ribofuranoside) 3,3′,5,5′-tetra-O-*p*-toluate. The simplicity of the nmr spectrum and comparison with published spectra of the α and β anomers of pyrimidine nucleosides of 3,5-di-O-toluoyl-2-deoxy-D-ribofuranose[5a] would appear to favor the β,β′ configuration for the product with both portions of the sugar having the same anomeric configuration and being in the furanose form.

The formation of this material can most easily be explained by the presence or generation of water during the coupling reaction between the purine mercury complex and the halo sugar (Scheme I).[5b] Normal

SCHEME I



precautions have been taken to predry the mercury complex and solvents by azeotropic distillation prior to the introduction of the chloro sugar; however, it may be that owing to less efficient agitation on a larger scale the removal of moisture was incomplete. A similar drying technique had been used for drying chloromercuri-6-chloropurine[6] for use in this reaction[7] on this scale, and in this instance a high yield of nucleosides was realized and only traces of the disaccharide were isolated. The alternate suggestion that water may be liberated during nucleoside formation in this reaction is rendered possible by the anomalous nature of the mercury complex of 2-acetamido-6-chloropurine[2] which comprises the addition of HgO_2 to 2-acetamido-6-chloropurine to give a complex of unknown structure. The high yields[2] (~57%) realized in the small-scale coupling reactions which were not achieved in the larger runs (25–40%) would tend to argue in favor of the moisture being of extraneous origin rather than being generated *in situ*. In this regard it is interesting to note that a similar product has recently been reported[8] to have been isolated from the reaction of tri-O-acetylxylopyranosyl bromide with various alcohols in the presence of mercuric acetate. The major side products in these instances, when moisture was not adequately removed, were postulated to be 1,1′-(β-D-xylopyranosyl-β-D-xylopyranoside) 2,2′,3,3′,4,4′-hexaacetate and D-xylopyranose 2,3,4-triacetate. The infrared spectra of our crude residues are lacking in significant absorption in the OH region and would tend to rule out the presence of 2-deoxy-D-ribofuranose 3,5-di-O-*p*-toluate in significant amounts in our material.

A second derivative of 3,5-di-O-*p*-toluoyl-2-deoxy-α-D-ribofuranosyl chloride has recently been isolated by Prystas and Sorm[4] as a side product from the Hilbert–Johnson reaction with 2,4-dimethoxy-5-fluoropyrimidine. This compound was assigned a bicyclo structure on the basis of chemical and spectral data wherein the elements of HCl were eliminated from C_1 and C_5 of the halo sugar. This material also regenerates 3,5-di-O-*p*-toluoyl-2-deoxy-α-D-ribofuranosyl chloride upon treatment with hydrogen chloride in glacial acetic acid. We do not have any evidence for the presence of this bicyclo compound in our residues.

Experimental Section

1,1′-(2-Deoxy-D-ribofuranosyl-2′-deoxy-D-ribofuranoside) 3,3′,5,5′-Tetra-O-*p*-toluate.—Using a previously described procedure[2] the mercury complex of 2-acetamido-6-chloropurine[2] (377 g, 0.85 mole) suspended in refluxing benzene (18 l.) was dried azeotropically by the distillation of 3–4 l. of solvent while stirring rapidly. With continued stirring the mixture was treated with 2-deoxy-α-D-ribofuranosyl chloride 3,5-di-O-*p*-toluate[3] (354 g, 0.91 mole). The coupling mixture was refluxed for 1 hr with vigorous stirring and filtered hot through a pad of Celite thereby removing the bulk of the unreacted mercury complex from which 2-acetamido-6-chloropurine could be recovered by treatment with aqueous potassium iodide followed by acidification with acetic acid.[2] The benzene filtrate was diluted with petroleum ether (50 l., bp 30–60°) and cooled to yield the crude mixed anomers of 2-acetamido-6-chloro-9-(2-deoxy-3,5-di-O-*p*-toluoyl-D-ribofuranosyl)purine which were purified and separated by an established process[2] to yield the β anomer (116.8 g, 24.5%) and the α anomer (75.7 g, 16%). The petroleum ether–benzene filtrate remaining from the precipitation of the nucleoside mixture was concentrated to a syrup *in vacuo*. The residue was taken up in chloroform (2 l.) and washed with 30% aqueous potassium iodide (0.5 l.) and water, and the organic layer was dried over anhydrous magnesium sulfate. The dried chloroform solution was concentrated to dryness *in vacuo* (35°) yielding a partially crystalline syrup (223 g). A portion of the residue (10 g) was crystallized from methanol to give the disaccharide as needles (0.4 g), mp 149–150°, $[\alpha]^{23.5}D$ −15° (*c* 1.0, $CHCl_3$). The crystalline solid appeared homogeneous by thin layer chromatography (silica gel–chloroform) and had the same R_f as that of a major component of the syrup. The infrared spectra of both the crude, syrupy residue and the crystalline

(4) M. Prystas and F. Sorm, *Collection Czech. Chem. Commun.*, **30**, 1900 (1965).

(5) (a) R. U. Lemieux and M. Hoffer, *Can. J. Chem.*, **39**, 110 (1961). (b) A referee has suggested that the primary by-product may actually be a labile purine–mercury–sugar complex which forms the disaccharide by hydrolysis during treatment of the coupling mixture with aqueous potassium iodide. We favor the simpler explanation that the compound is formed by the presence or generation of water during the reaction as stated above; however, a clear choice between the two alternatives cannot be made with the evidence at hand.

(6) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, Jr., *J. Org. Chem.*, **22**, 954 (1957).

(7) R. H. Iwamoto, E. M. Acton, and L. Goodman, *ibid.*, **27**, 3949 (1962).

(8) C. K. DeBruyne and F. G. Loontiens, *Nature*, **209**, 396 (1966).

solid showed the absence of OH absorption and closely resembled that of 1-O-methyl-2-deoxy-D-ribofuranoside 3,5-di-O-*p*-toluate.

The compound failed to react with bromine in carbon tetrachloride, and an osmometric molecular weight determination in benzene solution gave a value of 736 g/mole.

Anal. Calcd for $C_{42}H_{42}O_{11}$ (722.76): C, 69.78; H, 5.86; O, 24.36. Found: C, 69.88, C, 69.98; H, 5.59, H, 5.97; O, 24.75.

The nmr spectrum in $CDCl_3$ (TMS) showed the following signals (τ): 2.00, 2.08 pair of overlapping doublets (J = 8 cps) (four protons, aromatic), 2.76 broad doublet (J = 8 cps) (four protons, aromatic), 4.35 multiplet (two protons, $C_{1,3}$), 5.47 singlet (three protons, $C_{5,5'4}$), 7.62 singlet (eight protons, $2CH_3$, $C_{2,2'}$).

The entire syrupy carbohydrate residue was dissolved in glacial acetic acid (550 ml) and added to glacial acetic acid (750 ml) saturated with hydrogen chloride. The mixture was further saturated with hydrogen chloride and set to a mass of crystals which were recovered by filtration, washed thoroughly with ethyl ether, and vacuum dried (101.7 g) to give a recovery of 29% based on the starting weight of halo sugar. This material proved to be identical with that obtained by the method of Hoffer[3] on the basis of melting point, optical rotation, and identity of infrared spectra. A portion of the crystalline disaccharide (1.0 g) treated in the same manner also yielded the halo sugar (0.6 g) identical with an authentic sample.[3]

Acknowledgment.—We are pleased to acknowledge many helpful and stimulating discussions with Drs. Leon Goodman and Edward M. Acton, Stanford Research Institute, Menlo Park, California, and Dr. F. J. Petracek of these laboratories during the course of this work.

A Simplified Synthesis of 1-β-D-Arabinofuranosyl-5-fluorouracil[1]

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Received June 6, 1966

The synthesis of 1-β-D-arabinofuranosyl-5-fluorouracil (**1**) has been achieved by the coupling of monomercuri-5-fluorouracil[2] (**2**) with tri-O-benzoyl-D-ribofuranosyl chloride to form 5-fluoro-1-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)uracil[3] which was subsequently debenzoylated, converted to the 5′-O-trityl derivative, and tosylated in the 2′ position. The 2′-O-tosyl-5′-trityl derivative was converted to the 2,2′-anhydronucleoside which was opened to give the arabinofuranose configuration and detritylated yielding (**1**, 21% yield based on 5-fluorouracil). An alternate independent synthesis announced nearly simultaneously with the above,[4] and which was somewhat more direct in nature, involved the coupling of 2-O-acetyl-5-O-methoxycarbonyl-3-O-(*p*-toluenesulfonyl)-D-*xylo*-furanosyl chloride with **2**. The coupling product upon treatment with base was deacylated and formed an anhydronucleoside which on ion-exchange purification yielded the desired **1** in 16% over-all yield. Continued interest in the biological properties of **1** and its use as a precursor in the synthesis of the 5-fluorocytosine analog[5] has led to the very recent announcement[5] of an improved synthesis from 5-fluorouridine *via* 5′-O-trityl-5-fluorouridine which in turn was converted to the 2,2′-anhydro-5′-O-trityl derivative with the use of N,N-thiocarbonyldiimidazole. Opening of the anhydronucleoside and subsequent detritylation afforded **1** in recorded over-all yields in excess of 50% (based upon 5-fluorouracil).

The above syntheses are rather indirect in that the use of acyl blocking groups on the sugar moiety capable of participation in the heavy-metal condensation yields a nucleoside product possessing a predominantly 1,2-*trans* configuration.[6] Use of an acylated arabinofuranosyl halide in this synthesis would therefore yield mainly the undesired α anomer. The use of an α-haloarabinofuranosyl derivative blocked with nonparticipating (benzyl) groups[7] has led to an elegant synthetic method for preparing 9-β-D-arabinofuranosyladenine.[8] The extension of the use of this intermediate to the Hilbert–Johnson reaction for the preparation of the 1-β-D-arabinofuranosyl nucleosides of cytosine,[9] 5-trifluoromethyluracil,[9] and thymine[10] has been reported recently as well as an application of the mercuri method to the pyrimidine series in the synthesis of 1-β-D-arabinofuranosylcytosine.[9] We have investigated the synthesis of **1** by the Hilbert–Johnson method utilizing 2,4-diethoxy-5-fluoropyrimidine and 2,3,5-tri-O-benzyl-α-D-arabinofuranosyl chloride (**3**) and have found this method to be unsatisfactory in our hands.[10a] Use of **2**, however, proved a convenient way to prepare the desired compound. (See Scheme I.) The crude coupling reaction mixture, after removal of mercury, was debenzylated by hydrogenolysis under *acidic* conditions to avoid concurrent hydrogenolysis of the fluoro group. Excess acid was removed by slurrying with Dowex 2X8 (HCO_3^-) ion-exchange resin, and the rather acidic nucleoside (pK_a = 7.63[3]) was absorbed on Dowex 2X8 (OH^-) ion-exchange resin by a batchwise process.[4,11] Adsorption of the nucleoside was easily followed by thin layer chromatography as was the subsequent desorption with dilute acetic acid. The acetic acid solution of the nucleoside, free of neutral by-products, on concentration *in vacuo* afforded a foamed glass which on crystallization from ethanol gave **1** in an over-all yield of 30% based upon 5-fluorouracil. The product was isolated in a high state of purity, was chromatographically homogeneous

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-3764. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center.

(2) M. Hoffer, R. Duschinsky, J. J. Fox, and N. Yung, *J. Am. Chem. Soc.*, **81**, 4112 (1959).

(3) N. C. Yung, J. H. Burchenal, R. Fecher, R. Duschinsky, and J. J. Fox, *ibid.*, **83**, 4060 (1961).

(4) E. J. Reist, J. H. Osiecki, L. Goodman, and B. R. Baker, *ibid.*, **83**, 2208 (1961).

(5) J. J. Fox, N. Miller, and I. Wempen, *J. Med. Chem.*, **9**, 101 (1966).

(6) B. R. Baker, in Ciba Foundation Symposium, "Chemistry and Biology of Purines," 1957, p 120.

(7) C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **87**, 4636 (1965), and references cited therein.

(8) C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 3004 (1963).

(9) T. Y. Shen, H. M. Lewis, and W. V. Ruyle, *ibid.*, **30**, 835 (1965).

(10) F. Keller and A. R. Tyrrill, *ibid.*, **31**, 1289 (1966).

(10a) NOTE ADDED IN PROOF.—Subsequent to the submission of this manuscript proper conditions have been determined for the preparation of **1** by the Hilbert–Johnson method. Details will be described at a later date.

(11) We wish to thank Drs. L. Goodman and E. J. Reist, Stanford Research Institute, Menlo Park, Calif., for providing details of their purification procedure.