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]

F. KELLER, N. SUGISAKA, A. R. TYRRILL, L. H. BROWN, J. E. BUNKER, AND I. J. BOTVINICK

Medicinal Chemistry Section, Research Division, Riker Laboratories, Division of Rexall Drug and Chemical Company, Northridge California

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).

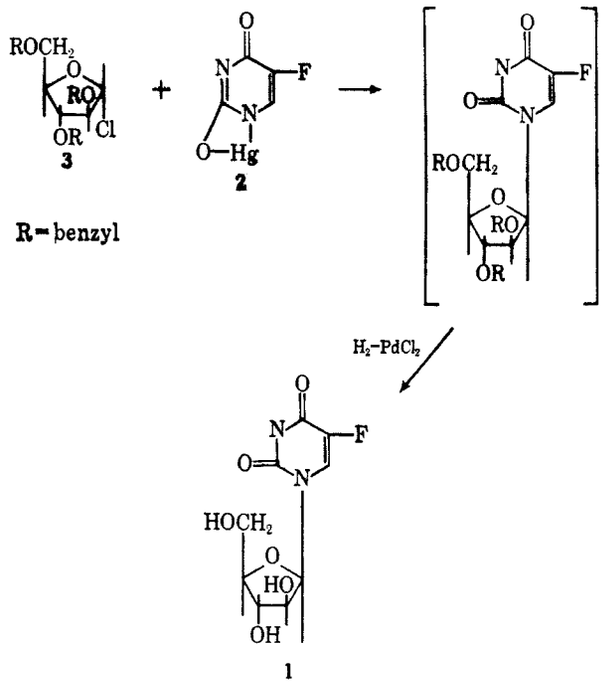
(9) T. Y. Shen, H. M. Lewis, and W. V. Ruyle, *ibid.*, **30**, 835 (1965).

(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.

SCHEME I



(tlc, paper chromatography), and had constants in good agreement with those appearing in the literature.[3-5]

Experimental Section

1-(β-D-Arabinofuranosyl)-5-fluorouracil (1).—2,3,5-Tri-O-benzyl-1-(*p*-nitrobenzoyl)-D-arabinofuranose[12] (56.96 g, 0.1 mole), prepared in 90% yield from 2,3,5-tri-O-benzyl-β-D-arabinofuranose,[13] was added to dry methylene chloride (700 ml) which had been saturated with hydrogen chloride at 0°. The solution was maintained at 0° for 3 hr while protecting from moisture and maintaining a slow stream of hydrogen chloride through the reaction mixture. The *p*-nitrobenzoic acid which had separated in quantitative yield was removed by rapid filtration through a sintered glass funnel and the filtrate was concentrated to dryness *in vacuo* (bath 35°) and evacuated (0.1 mm) for 16 hr (25°). Monomercuri-5-fluorouracil[2,14] (16.43 g, 0.05 mole) was suspended in toluene (1 l.) and dried azeotropically by the distillation of a portion of the solvent (250 ml). A second portion of distillate (250 ml) was reserved for use in transferring the chloro sugar to the slightly warm, dried suspension of monomercuri-5-fluorouracil. Heating and stirring while protecting from moisture was recommended upon addition of the halo sugar. The mixture was refluxed for 15 min yielding a nearly clear solution which was cooled rapidly (ice bath) and filtered from a trace of insolubles. The filtrate was washed with 30% aqueous potassium iodide (two 250-ml portions) and water (250 ml), stirred with saturated sodium bicarbonate (500 ml) for 30 min, and washed with water (500 ml). The dried (magnesium sulfate) organic layer was concentrated to dryness *in vacuo* (30° bath) yielding a brown oil (50 g) which was debenzylated without further purification. The residual oil was dissolved in dry methanol (400 ml) and hydrogenated in two batches, each being added to palladium chloride (10.5 g) which had been suspended in dry methanol and prereduced just prior to the addition of the blocked nucleoside. The hydrogenation was carried out at an initial pressure of 3 atm, reduction being complete in approximately 40 min. The hydrogenation mixtures were filtered free of catalyst and the filtrates were brought to pH 5.5 by stirring with Dowex 2X8 (HCO_3^-) ion-exchange resin. The resin was removed by filtration and washed with methanol, and the combined filtrates and washings were concentrated to dryness *in vacuo* (35° bath) yielding a brown oil (21.6 g). The residue was dissolved in a 25:15 methanol–water mixture (400 ml) and stirred with freshly prepared Dowex 2X8 (OH^-) ion-exchange resin. After 15 min the supernatant appeared free of nucleoside by thin layer chromatography (silica gel; benzene–*n*-butylamine–water, 15:5:1). The resin was removed by filtration and washed with water until the washings were neutral (the filtrate and washings being discarded). The nucleoside was eluted from the resin by treatment with 5% acetic acid (six 200-ml portions) each portion being stirred for 10 min and the progress of the elution followed by thin layer chromatography. The combined acetic acid solutions were clarified by filtration through Celite and concentrated to dryness *in vacuo* (35° bath). Absolute ethanol (two 20-ml portions) was added to the residue and removed *in vacuo* to effect a final drying of the residue which was obtained as a foamed glass (10 g). This material on solution in ethanol (40 ml) and chilling afforded the product (I) as colorless crystals: 3.92 g, 30.2%, mp 183–185°, $[\alpha]^{26.0}D$ +129.4° (*c* 0.2, H_2O) [lit.[3,4] mp 187–188°, $[\alpha]^{24}D$ +128° (H_2O)]. On concentration of the mother liquors a second crop (0.282 g, 2.1%) was obtained: mp 176–179°. The material was homogeneous on paper chromatography (*n*-BuOH–H_2O, R_f 0.42) and showed the absence of 1-β-D-arabinofuranosyluracil (R_f 0.32). A portion of the first crop material was recrystallized from ethanol to yield the analytical sample: mp 184–186°, $[\alpha]^{26.0}D$ +125.0° (*c* 0.2, H_2O); $\lambda_{max}^{0.1\ N\ HCl}$ 270 mμ (ε 8900), $\lambda_{min}^{0.1\ N\ HCl}$ 234 mμ (ε 1310), $\lambda_{max}^{pH\ 7}$ 270 mμ (ε 8460), $\lambda_{min}^{pH\ 7}$ 237 mμ (ε 2990), $\lambda_{max}^{0.1\ N\ NaOH}$ 272 mμ (ε 7470), $\lambda_{min}^{0.1\ N\ NaOH}$ 247 mμ (ε 4030) [lit.[4] $\lambda_{max}^{pH\ 1}$ 270 mμ (ε 9080), $\lambda_{max}^{pH\ 7}$ 270 mμ (ε 8670), $\lambda_{max}^{pH\ 13}$ 272 mμ (ε 7590)].

Anal. Calcd for $C_9H_{11}FN_2O_6$ (262.2): C, 41.22; H, 4.23; F, 7.25; N, 10.68. Found: C, 40.91; H, 4.30; F, 7.41; N, 10.45.

(12) R. Barker and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 4608 (1961).
(13) Pfanstiehl Laboratories, Inc., Waukegan, Ill.
(14) The 5-fluorouracil used in this work was generously provided by Hoffmann LaRoche, Inc., Nutley, N. J.

Anomeric Equilibria in Derivatives of Amino Sugars. 2-Amino-2-deoxy-D-mannose Hydrochloride[1,2]

DEREK HORTON, JON S. JEWELL, AND KERSTIN D. PHILIPS

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received May 13, 1966

Crystalline 2-amino-2-deoxy-D-mannose hydrochloride[3] differs from other crystalline 2-amino-2-deoxy-D-hexose hydrochlorides[4] in that it has not been observed to exhibit mutarotation in water or dilute hydrochloric acid.[3-11] The observed specific rotation is about −3°. It has been proposed[12] that the molecule is stabilized as the β-D anomer in the *C1* chair conformation (2), by the formation of hydrogen bonds between hydrogens of the (axial) ammonium group at C-2 and the equatorial oxygen atoms at C-1 and C-4, with the result that conversion into the α-D anomer (1) is prevented. It has been pointed out[13] that a hydrogen bond from the am-

(1) Supported in part by Grants-in-Aid No. 19187 and 170200 from The Ohio State University Development Fund.
(2) Funds for purchase of the nmr spectrometer were provided by the National Science Foundation, Washington, D. C.
(3) P. A. Levene, *J. Biol. Chem.*, **39**, 69 (1919).
(4) R. Kuhn, W. Bister, and H. Fischer, *Ann.*, **617**, 109 (1958).
(5) P. A. Levene, "Hexosamines and Mucoproteins," Longmans, Green and Co., London, 1925, p 16.
(6) R. Kuhn and W. Bister, *Ann.*, **602**, 217 (1957).
(7) D. G. Comb and S. Roseman, *Biochim. Biophys. Acta*, **29**, 653 (1958).
(8) C. T. Spivak and S. Roseman, *J. Am. Chem. Soc.*, **81**, 2403 (1959).
(9) A. N. O'Neill, *Can. J. Chem.*, **37**, 1747 (1959).
(10) R. Kuhn and J. C. Jochims, *Ann.*, **628**, 172 (1959).
(11) J. C. Sowden and M. L. Oftedahl, *J. Am. Chem. Soc.*, **82**, 2303 (1960).
(12) M. J. Carlo, A. Cosmatos, and H. K. Zimmerman, Jr., *Ann.*, **650**, 187 (1961).
(13) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 421.