Nucleosides I. A New Synthesis of 1-β-D-Arabinofuranosyl Pyrimidine Nucleosides

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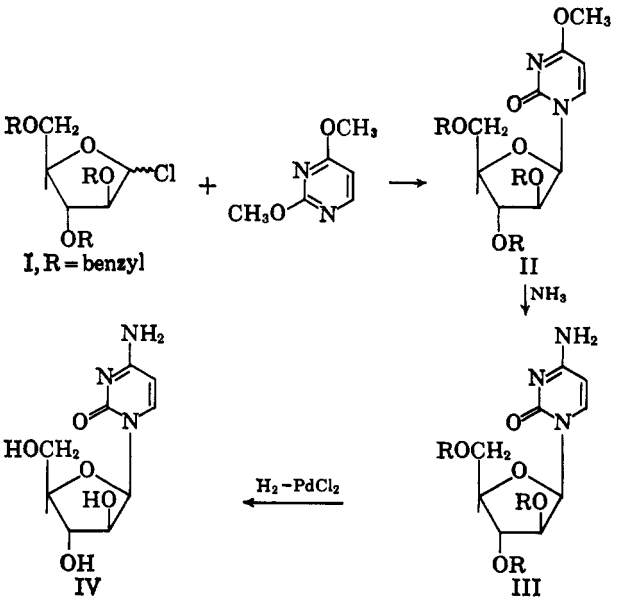
Condensation of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride with 2,4-dimethoxypyrimidine, followed by amination and debenzylation, has afforded 1-β-D-arabinofuranosylcytosine in *ca.* 50% over-all yield. 1-β-D-Arabinofuranosyl-5-trifluoromethyluracil was prepared in a similar manner.

Interest in arabinosyl pyrimidines as potential chemotherapeutic agents was stimulated recently by the observation that 1-β-D-arabinofuranosylcytosine (cytosine arabinoside) was found to have some selective antiviral activity *vs.* DNA viruses such as herpes simplex and vaccinia.[1] Although the syntheses of several so-called "spongo" pyrimidine nucleosides,[2] such as 1-β-D-arabinofuranosyluracil,[3] -thymine,[4] -cytosine,[5,6] and -N-methylcytosine,[6] have been described, multiple-step conversions from the corresponding ribonucleosides, often *via* the O^2,2′-cyclonucleosides, are generally involved. Condensation of an acylated arabinosyl halide with pyrimidines, in a manner analogous to the formation of ribo- or 2′-deoxyribofuranosides, would not be expected to favor the formation of a β-nucleoside because of the configuration of the 2′-hydroxy group.[7] In the search of a general method for the preparation of various 1-β-D-arabinofuranosylpyrimidines, our attention was directed to compound I, 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride, reported recently by Glaudemans and Fletcher.[8,9] This communication describes the application of this reagent to the synthesis of pyrimidine nucleosides; a convenient synthesis of 1-β-D-arabinofuranosylcytosine has been achieved.

As discussed by Glaudemans and Fletcher,[8,9] the formation of a "*cis* nucleoside" in an apparently stereospecific manner is attributable to Walden inversion at C-1′ during the condensation of the 2′,3′,5′-tri-*O*-benzyl-D-arabinofuranosyl chloride, presumably of the α-configuration, with the adenine moiety following a SN2 mechanism. In our studies, for the purpose of preserving the essential SN2 character of the condensation reaction, we have used excess 2,4-dimethoxypyrimidine as the nucleophile with methylene chloride as the solvent. The reaction was carried out at room temperature, and the progress was followed to completion by thin layer chromatography. After 3 days, the reaction mixture was evaporated *in vacuo* to give a sirupy product which was essentially 1-(2′,3′,5′-tri-*O*-benzyl-β-D-arabinofuranosyl)-4-methoxy-2(1*H*)-pyrimidone (II) as judged by its physical characteristics. The presence of the α-anomer, if any, was not detected by chromatographic and n.m.r. studies.[10] Further purification of the sirupy II was not deemed necessary, since, upon treatment with concentrated ammonia[11] in methanol at 100°, the crystalline cytosine derivative III, m.p. 153–154°, readily separated from the amination mixture in 68% yield. The benzyl groups in III were smoothly removed by hydrogenolysis in methanol in the presence of prereduced palladium chloride as a catalyst. Since the reduction mixture was relatively acidic, expedient neutralization with ion-exchange resins after the hydrogenolysis was found to be highly advisable. After evaporation and crystallization, pure 1-β-D-arabinofuranosylcytosine (IV), m.p. 212–213°,



$[\alpha]^{24}D$ +153°, was obtained in 80% yield. The structure of this product was confirmed by direct comparison of its hydrochloride with an authentic sample[12] and by deamination with nitrous acid to 1-β-D-arabinofuranosyluracil, identical with a sample prepared by another route.[13] Without further study of conditions, the over-all yield of IV from the arabinosyl chloride was *ca.* 50%.

(1) H. E. Ronis and H. G. Johnson, *Bact. Proc.*, **45**, 140 (1962); G. E. Underwood, *Proc. Soc. Exptl. Biol. Med.*, **111**, 660 (1962); H. E. Kaufman and E. D. Maloney, *Arch. Ophth.*, **69**, 626 (1963).

(2) W. Bergmann and D. F. Burke, *J. Org. Chem.*, **20**, 201 (1955); G. R. Barker and G. E. Foll, *J. Chem. Soc.*, 3794 (1957).

(3) D. M. Brown and A. R. Todd, *ibid.*, 52 (1952); D. M. Brown, A. R. Todd, and S. Varadarajan, *ibid.*, 2388 (1956).

(4) R. Markham and J. D. Smith, *Biochem. J.*, **52**, 552 (1952); J. J. Fox, N. Yung, and A. Bendich, *J. Am. Chem. Soc.*, **79**, 2775 (1957).

(5) E. R. Walwick, W. K. Roberts, and C. A. Dekker, *Proc. Chem. Soc.*, 84 (1959).

(6) J. H. Hunter, U. S. Patent 3,116,282 (Dec. 1963).

(7) For recent reviews, see J. J. Fox and I. Wempen, *Advan. Carbohydrate Chem.*, **14**, 283 (1959); A. M. Michelson, "The Chemistry of Nucleosides and Nucleotides," Academic Press Inc., New York, N. Y., 1963, pp. 1–97; T. L. V. Ulbricht, *Angew. Chem., Intern. Ed. Engl.*, **1**, 476 (1962).

(8) C. P. J. Glaudemans and H. G. Fletcher, Jr., Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1963, p. 20D.

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

(10) The measurement and interpretation of n.m.r. spectra were carried out by Dr. Nelson Trenner and Mr. B. Arison of these laboratories.

(11) Anhydrous ammonia in methanol gave similar results.

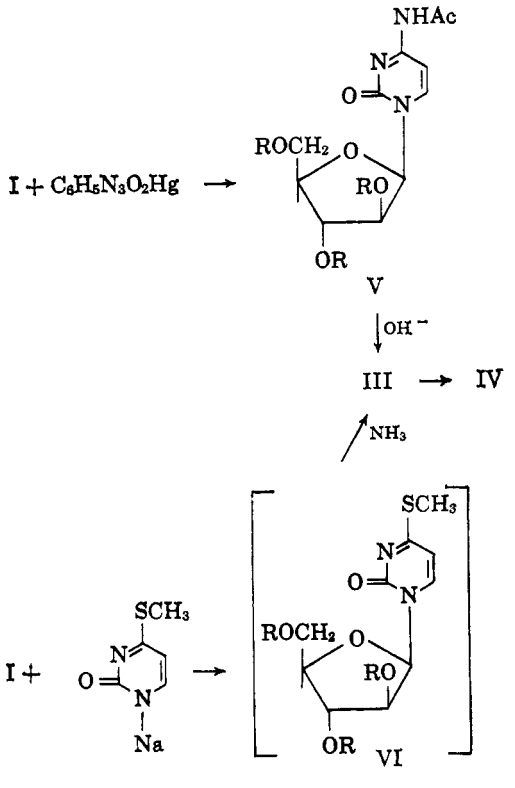
(12) We are indebted to Dr. H. D. Wood, Jr., of Cancer Chemotherapy National Service Center, National Institutes of Health, for a sample of 1-β-D-arabinofuranosylcytosine hydrochloride.

(13) To be published at a later date.

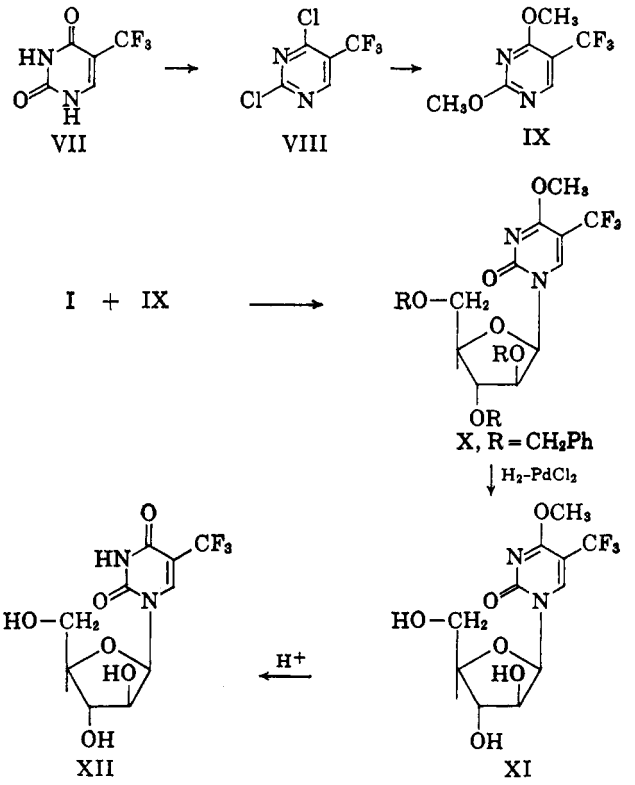
As in the formation of 9-β-D-arabinofuranosyladenine,[8] a high degree of stereospecificity in the condensation of I with 2,4-dimethoxypyrimidine to form a "*cis*" pyrimidine nucleoside was demonstrated.

In another experiment when the condensation with I was carried out at 100°,[14] the yield of II was reduced to *ca.* 45%, again characterized as the crystalline derivative III by ammonolysis. In addition, a by-product containing an altered pyrimidine moiety was obtained in *ca.* 25% yield, but its structure remains to be elucidated.

Instead of 2,4-dimethoxypyrimidine, the mercury derivative of *N*-acetylcytosine[15] and the sodio derivative of 4-methylmercapto-2-pyrimidone[16] were also tried as nucleophiles in the condensation with I. In each case, the crystalline derivative III was obtained after appropriate transformations; however, the results of these preliminary experiments indicated that the condensations were less satisfactory.



A similar sequence of reactions was used for the synthesis of 5-trifluoromethyl-1-β-D-arabinofuranosyluracil (XII). This compound is of interest because of the reported biological activity of 5-trifluoromethyl-2′-deoxyuridine.[17,18] The required 2,4-dimethoxy-5-trifluoromethylpyrimidine (IX) was made *via* the dichloro compound (VIII) by standard methods. Condensation of IX with I yielded X as a sirup, which was not purified, but was debenzylated to give XI as a crystalline solid. Treatment of XI with methanolic hydrogen chloride yielded XII.



The lability under alkaline conditions of the CF_3 group in 5-trifluoromethyluracil has been reported by Heidelberger.[17] It has been found that XII is likewise unstable at pH 12, the ultraviolet absorption maximum changing from 262.5 to 267.5 mμ in 1 hr. and to 272.0 mμ after 24 hr.

Further study of this versatile reagent (I) is in progress.

Experimental[19,20]

1-(2′,3′,5′-Tri-*O*-benzyl-β-D-arabinofuranosyl)-4-methoxy-2-(1*H*)-pyrimidinone (II). **A.**—An excess of 2,4-dimethoxypyrimidine[21] (17.36 g., 0.124 mole), dissolved in 50 ml. of dry methylene chloride, was added to 25.9 g. (0.0591 mole) of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (I) in 800 ml. of methylene chloride which had been dried over magnesium sulfate and filtered directly into the reaction vessel. The halo sugar was prepared[8] from an anomeric mixture of the *p*-nitrobenzoyl ester[22] of 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose.[23] The solution, protected by a calcium sulfate drying tube, was stirred gently at room temperature for 3 days.

The solvent was removed from the faintly amber condensation product *in vacuo* at a bath temperature below 45° to give 41.5 g. of a mixture of II and dimethoxypyrimidine. A small sample of the crude product was adsorbed on a column of acid-washed alumina and eluted with ethyl acetate. The oily product showed $[\alpha]^{26}D$ +115° (methylene chloride, *c* 2.0), λ_{max}^{MeOH} 276 mμ (ε 6401), λ_{min} 244 mμ.

Anal. Calcd. for $C_{31}H_{32}N_2O_6$: C, 70.45; H, 6.10; N, 5.30. Found: C, 69.41; H, 6.08; N, 5.23.

B.—A condensation at elevated temperature without solvent was carried out as previously described, except the mixture was kept at 100° in an oil bath for 20 hr. The crude reaction mixture was chromatographed on a column of acid-washed alumina using ethyl acetate as the eluent. In addition to the desired product a second, faster running compound was obtained which

(14) Fusion of a glycosyl halide with 2,4-dialkoxypyrimidine at elevated temperature is generally used in the Hilbert–Johnson reaction.

(15) J. J. Fox, N. Yung, I. Wempen, and I. L. Doerr, *J. Am. Chem. Soc.*, **79**, 5063 (1957).

(16) Kindly provided by Dr. B. O. Linn of these laboratories.

(17) C. Heidelberger, D. G. Parsons, and D. C. Remy, *J. Med. Chem.*, **7**, 1 (1964).

(18) H. E. Kaufman and C. Heidelberger, *Science*, **145**, 585 (1964).

(19) All melting points were determined on a Kofler hot stage equipped with a calibrated thermometer.

(20) We are indebted to Mr. R. N. Boos and his associates for the microanalytical data.

(21) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 2004 (1930).

(22) R. Barker and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 4608 (1961).

(23) S. Tejima and H. G. Fletcher, Jr., *ibid.*, **28**, 3001 (1963).

amounted to approximately 25% of the product, $[\alpha]^{25}D$ +34° (dichloromethane, *c* 2.0), λ_{max}^{MeOH} 264, 208 mμ ($E^{1\%}_{1cm}$ 152, 612). Alteration of the pyrimidine chromophore was confirmed by n.m.r. studies.

Anal. Found: C, 71.07; H, 6.00; N, 5.11.

1-(2′,3′,5′-Tri-*O*-benzyl-β-D-arabinofuranosyl)cytosine (III).—The crude condensation mixture (39 g.) from A was transferred to a Carius tube with 190 ml. of anhydrous methanol to which 190 ml. of concentrated ammonium hydroxide was added. The tube was sealed and heated at 100° for 17 hr. in a bomb.[15]

The crystalline product was separated from the reaction mixture by filtration. The ammonolysis by-product from the excess dimethoxypyrimidine remained in the filtrate.

Recrystallization from 225 ml. of hot ethyl acetate afforded 19 g. (68% over-all from II) of the desired product, m.p. 153–154°, $[\alpha]^{24}D$ +123° (methylene chloride, *c* 2.0), λ_{max}^{MeOH} 272.5, 232.5 mμ (ε 8635, 7504), λ_{min} 254 mμ.

Anal. Calcd. for $C_{30}H_{31}N_3O_5$: C, 70.16; H, 6.08; N, 8.18. Found: C, 70.24; H, 5.92; N, 8.33.

1-β-D-Arabinofuranosylcytosine (IV).—To 5.0 g. of pre-reduced palladium[8,9] chloride suspended in 1000 ml. of anhydrous methanol, 5.14 g. (0.01 mole) of thoroughly dried 1-(2′,3′,5′-tri-*O*-benzyl-β-D-arabinofuranosyl)cytosine dissolved in 100 ml. of methanol was added. In 11 min. the theoretical amount of hydrogen was absorbed by the acidic solution. The catalyst was removed by filtration, and the filtrate was stirred with 125 ml. of Dowex 2-X8 (HCO_3^-) which had been previously prepared. Then the resin was filtered from the neutral solution, and the solvent was removed *in vacuo*.

The crystalline product was dissolved in water and filtered in order to remove contaminating colored impurities which presumably came from the resin. After concentration to near dryness *in vacuo* the cytosine arabinoside crystallized spontaneously and was filtered with the aid of 15 ml. of ethanol, 1.96 g., 80%: m.p. 212–213°, $[\alpha]^{24}D$ +153° (water, *c* 0.5); lit.[5] m.p. 212–213°, $[\alpha]D$ +158°); ultraviolet spectra: pH 2, λ_{max} 281.0, 212.5 mμ (ε 13,171, 10,230), λ_{min} 241 mμ; pH 12, λ_{max} 272.5 mμ (ε 9259), shoulder at 227 mμ (ε 8311), λ_{min} 250.5 mμ.

Anal. Calcd. for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28. Found: C, 44.85; H, 5.41; N, 17.35.

Condensation of I with Mercury Derivative of *N*-Acetylcytosine. A. 4-*N*-Acetyl-1-(2′,3′,5′-tri-*O*-benzyl-β-D-arabinofuranosyl)cytosine (V).—Sirupy 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (4.39 g., 0.01 mole), prepared by the method described by Glaudemans and Fletcher[8] from 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose[15] (4.21 g., 0.01 mole), was dissolved in 65 ml. of freshly distilled toluene and added in two portions to a refluxing suspension of thoroughly dried *N*-acetylcytosinemercury[23] in 100 ml. of toluene. Just before adding the halide, the suspension was dried by azeotropic distillation of solvent (30 ml.) from 130 ml. of toluene and the *N*-acetylcytosinemercury, 1.76 g. (0.005 mole), contained in the reaction flask. A clear solution was obtained after the mixture was refluxed with vigorous stirring for 30 min. After cooling, the solution was poured into 500 ml. of petroleum ether and allowed to stand overnight in a refrigerator at 5°.

Since crystallization did not occur, the solution was concentrated *in vacuo* to a thin sirup, which was dissolved in 200 ml. of chloroform, washed with 25 ml. of 30% potassium iodide and 25 ml. of water, dried over magnesium sulfate, and reconcentrated to give 5.18 g. of a crude sirup. The product was shown to be a mixture by thin layer chromatography, and it was chromatographed and separated on 250 g. of silica gel using a 50% ethyl acetate–benzene solvent system. One large fraction (3.0 g.) and several trace fractions were eluted from the column before the desired product was recovered as a sirup (0.80 g.), λ_{max}^{MeOH} 300, 248 mμ (ε 7334, 14,168), λ_{min} 273.5 mμ.

Anal. Calcd. for $C_{32}H_{33}N_3O_6$: C, 69.17; H, 5.98; N, 7.56. Found: C, 68.77; H, 5.80; N, 7.36.

B. 1-(2′,3′,5′-Tri-*O*-benzyl-β-D-arabinofuranosyl)cytosine (III).—Purified 4-*N*-acetyl-1-(2′,3′,5′-tri-*O*-benzyl-β-D-arabinofuranosyl)cytosine (0.80 g., 1.44 moles) was dissolved in 8 ml. of ethanol, 3.1 ml. of 1 *N* sodium hydroxide was added, and the mixture was heated with stirring at 70–80° for 30 min.[24]

When the solution had cooled, the product was extracted with chloroform and dried over magnesium sulfate, and the solvent was removed. The residue was crystallized twice from ethyl acetate (325 mg., 44%), m.p. 148–151°, $[\alpha]^{23}D$ +117.9° (methylene chloride, *c* 2.0), λ_{max}^{MeOH} 273.0, 232.5 mμ (ε 8944, 7453), λ_{min} 254 mμ. The infrared spectrum (Nujol mull) was the same as that of the sample prepared *via* II.

Anal. Calcd. for $C_{30}H_{31}N_3O_5$: C, 70.16; H, 6.08; N, 8.18. Found: C, 69.83; H, 6.10; N, 8.27.

C. 1-β-D-Arabinofuranosylcytosine (IV).—Palladium chloride (120 mg.) suspended in 75 ml. of anhydrous methanol was reduced with hydrogen at room temperature, then 150 mg. of 1-(2′,3′,5′-tri-*O*-benzyl-β-D-arabinofuranosyl)cytosine dissolved in 25 ml. of dry methanol was added to the suspension. The mixture was hydrogenated at room temperature. After removal of the catalyst by filtration, the acidic solution was passed through a column prepared from 6 ml. of Dowex 2-X8 (HCO_3^-), and the neutral eluent was concentrated *in vacuo*. Purified starting material (100 mg.) was recovered with a higher melting point, 154–156°.

The hydrogenolysis was successfully repeated using 100 mg. of palladium chloride suspended in 20 ml. of dry methanol just as described above, except the hydrogenation proceeded overnight (24 hr.) before theoretical hydrogen absorption (13.2 ml.) was realized.

The product was worked up as previously described, dissolved in hot 50% aqueous methanol, and filtered in order to remove some insoluble material. After removal of the solvent *in vacuo*, the hard glass was crystallized by trituration with a small amount of ethanol yielding 23 mg., 50%: m.p. 212–213°; $[\alpha]^{24}D$ +129° (water, *c* 0.5); ultraviolet absorption data: pH 2, λ_{max} 280, 212 mμ (ε 12,758, 9182), λ_{min} 242 mμ; pH 12, λ_{max} 272 mμ (ε 8602), shoulder at 227.0 mμ (ε 7630), λ_{min} 250 mμ.

Anal. Calcd. for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28. Found: C, 43.53; H, 5.01; N, 16.57.

1-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-4-methylthiopyrimidin-2-one (VI).—To a stirred suspension of 0.131 g. of a 50% emulsion of sodium hydride in mineral oil (2.8 moles) in 15 ml. of dry dimethylformamide was added 0.403 g. (2.8 moles) of 4-methylthiopyrimidin-2-one.[16] A solution of 1.2 g. (2.8 moles) of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride in 10 ml. of dimethylformamide was added, and the mixture was stirred at room temperature for 18 hr. The mixture was treated with 100 ml. of cold water and extracted with ether. The ether solution was washed with water, dried over magnesium sulfate, and concentrated to a yellow oil, 1.43 g. Chromatography on 50 g. of silica gel furnished 1.34 g. in one peak, eluted with ether. Attempts at recrystallization were not successful.

1-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-4-aminopyrimidin-2-one (III).—A mixture of 120 mg. of the 4-thio compound (VI), 15 ml. of methanol, and 15 ml. of liquid ammonia was heated in a bomb at 100° for 12 hr. After evaporation of the solvent, the residue was triturated with ether–ethyl acetate, and then recrystallized from ethyl acetate to obtain 10.5 mg. of product, m.p. 150–155°, not depressed when mixed with a specimen prepared from II. The infrared spectra (Nujol mull) of the two samples were identical.

2,4-Dichloro-5-trifluoromethylpyrimidine (VIII).—To 5.0 g. (0.0277 mole) of 5-trifluoromethyluracil (VII),[25] suspended in 20 ml. of phosphorus oxychloride, 4.9 g. of *N*,*N*-diethylaniline was added. The mixture was heated at reflux in an oil bath for 23 hr., cooled, concentrated to 10 ml. *in vacuo*, and poured into 20 g. of ice. After vigorous agitation to complete the decomposition of excess phosphorous oxychloride, the mixture was extracted four times with 50-ml. portions of ether, which were combined and washed successively with 30 ml. of sodium bicarbonate and 20 ml. of water. The ether solution was dried over calcium chloride and concentrated by distillation through an 18-in. Vigreux column at atmospheric pressure. The last 10 ml. was removed carefully *in vacuo*. Distillation at slightly reduced pressure yielded 3.5 g. (58%) of a light yellow oil, b.p. 126° (650 mm.), λ_{max}^{MeOH} 266, 213 mμ (ε 2452, 9309), λ_{min} 237 mμ.

Anal. Calcd. for $C_5H_1Cl_2F_3N_2$: C, 27.66; H, 0.47; Cl, 32.67; F, 26.27. Found: C, 28.57; H, 0.58; Cl, 32.62; F, 27.7.

This material was used without further purification.

2,4-Dimethoxy-5-trifluoromethylpyrimidine (IX).—A solution of 2,4-dichloro-5-trifluoromethylpyrimidine, 3.16 g. (0.0145 mole) in 7 ml. of anhydrous methanol was added dropwise to a stirred solution of sodium methoxide, 1.57 g. (0.0290 mole), dissolved in 10 ml. of methanol. Sodium chloride immediately

(24) J. F. Codington and J. J. Fox, *Methods Carbohydrate Chem.*, **2**, 116 (1963).

(25) M. P. Mertes and S. E. Saheb, *J. Pharm. Sci.*, **52**, 508 (1963).

separated from the solution which became warm as the addition was made. After stirring the suspension for 30 min. longer, the sodium chloride was filtered off (99% yield), and the filtrate was concentrated to 10 ml. by distilling the solvent through a Vigreux column at atmospheric pressure. The residue was dissolved in 60 ml. of ether, washed with 7 ml. of 20% sodium hydroxide and 7 ml. of water, and dried over sodium sulfate. The solvent was removed by distillation through a Vigreux column, the last of the solvent being removed carefully under slight vacuum. The residual solid was recrystallized by dissolving in a minimum amount of petroleum ether and chilling the solution in Dry Ice: yield 2.90 g. (96%), m.p. 55–56°, λ_{max}^{MeOH} 257, 216 mμ (ε 5366, 9817), λ_{min} 236.5 mμ.

Anal. Calcd. for $C_7H_7F_3N_2O_2$: C, 40.39; H, 3.39; F, 27.39; N, 13.45. Found: C, 40.89; H, 3.06; F, 25.31; N, 13.29.

This compound sublimes readily even at room temperature, and must be kept in well-sealed containers.

2′,3′,5′-Tri-*O*-benzyl-1-β-D-arabinofuranosyl-4-methoxy-5-trifluoromethyl-2-(1*H*)pyrimidinone (X).—Methylene chloride (80 ml.), which had been dried over magnesium sulfate, was filtered directly into a dry flask containing 5.60 g. (0.0128 mole) of 2′,3′,5′-tri-*O*-benzylarabinofuranosyl chloride (I). A solution of 2,4-dimethoxy-5-trifluoromethylpyrimidine (IX, 2.66 g., 0.0128 mole) in 20 ml. of methylene chloride was dried over sodium sulfate and filtered directly into the reaction vessel. The solution was stirred gently for 3 days at room temperature, protected by a drying tube. After removal of solvent, the crude product, 7.5 g. (quant.), was used without purification in the following step.

1-β-D-Arabinofuranosyl-4-methoxy-5-trifluoromethyl-2(1*H*)-pyrimidinone (XI).—Two grams of the crude condensation product was dissolved in 90 ml. of dry methanol (Molecular Sieves) and added to 2 g. of palladium chloride which had been suspended and pre-reduced in 60 ml. of anhydrous methanol. The theoretical hydrogen absorption was observed after 3 min. shaking at room temperature. After removal of the catalyst by filtration the acidic solution was neutralized batchwise with Dowex 2-X8 (HCO_3^-) and filtered. When the solvent was removed *in vacuo*, spontaneous crystallization occurred. The product was triturated with water, filtered, and washed several times in order to remove contaminant arabinofuranose. Recrystallization was accomplished by dissolving in the minimum amount of methanol, adding an equal volume of ether and excess hexane, to yield 0.720 g. (66%) of pure product: m.p. 184–186°; $[\alpha]_D$ +133.4° (*c* 0.5, MeOH); ultraviolet spectra: pH 2, λ_{max} 270, 205 mμ (ε 5933, 18,006), λ_{min} 238 mμ; pH 12, λ_{max} 278, 217 mμ (ε 6390, 12,812), inflection at 225 mμ (ε 12,290), λ_{min} 255 mμ.

Anal. Calcd. for $C_{11}H_{13}F_3N_2O_6$: C, 40.50; H, 4.02; F, 17.47; N, 8.58. Found: C, 40.68; H, 3.80; F, 17.3; N, 8.52.

5-Trifluoromethyl-1-β-D-arabinofuranosyluracil (XII).—To 5 ml. of 1.1 *N* methanolic hydrogen chloride 160 mg. of 1-β-D-arabinofuranosyl-4-methoxy-5-trifluoromethyl-2(1*H*)-pyrimidinone (XI) was added. The solution, in a tightly stoppered flask, was kept at room temperature for 3 days. After concentration *in vacuo* the residue was dissolved in a minimum amount of methanol, diluted with ether, and crystallized by addition of hexane. After one recrystallization 125 mg. (82%) of the pure product was obtained: m.p. 225–227°; $[\alpha]_D$ +76° (*c* 0.5, water); ultraviolet spectra: pH 2, λ_{max} 262.5, 205 mμ (ε 10,296, 8923), λ_{min} 228 mμ; pH 12, immediately after dissolving, λ_{max} 262.5 mμ (ε 7020), λ_{min} 241 mμ; after 1 hr., λ_{max} 267.5 mμ (ε 7238), λ_{min} 247.5 mμ; after 24 hr., λ_{max} 272 mμ (ε 8170), λ_{min} 249.5 mμ.

Anal. Calcd. for $C_{10}H_{11}F_3N_2O_6$: C, 38.47; H, 3.55; F, 18.25; N, 8.89. Found: C, 38.11; H, 3.81; F, 19.4; N, 8.80.

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The Structure of Osazones[1]

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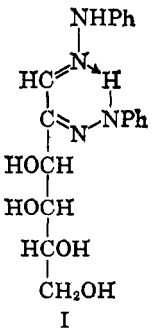
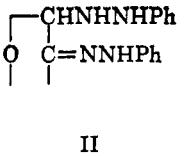
The n.m.r. spectra of D-*lyxo*-hexose phenylosazone (I) and its tetraacetate (IV) show two imino protons, indicating that both compounds have acyclic sugar chains. A range of mono-*N*-benzoylated poly-*O*-benzoylated osazones (IXa–f) described herein showed only one, low-field imino proton resonance, as did D-*arabino*-hexosulose 1-(methylphenylhydrazone) 2-(phenylhydrazone) tetraacetate (VI), indicating that the *N*-benzoyl group in (IXa–f) is attached to the hydrazone residue at C-1. For the same reason, structure X was assigned to *N*-acetyl-di-*O*-acetyl-3,6-anhydro-D-*ribo*-hexose phenylosazone.

Various cyclic structures have been suggested[3] for osazones to explain their mutarotation, the different reactivity of their two hydrazone residues,[4] and the difference in their behavior toward nitrous acid as compared with their acyclic acetates.[5] In the present work n.m.r. spectroscopy was used to determine whether osazones exist mainly in the acyclic form (I) which possesses two imino protons or in one of the two cyclic forms (II or III) which possess three.

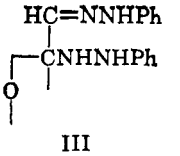
The n.m.r. spectrum of the acyclic D-*lyxo*-hexose phenylosazone tetraacetate (IV) in $CDCl_3$ was first determined by Wolfrom, Fraenkel, Lineback, and Komitsky[6] and provided direct evidence for the chelated



I



II



III

structure originally proposed, without experimental evidence, by Fieser and Fieser.[7] The spectrum showed two peaks at τ −2.48 and 1.58 which were attributed[6] to the two imino protons and the aldimine proton of C-1, respectively. Since both peaks disappear on deuteration (Figure 1), we have now assigned them both to the

(1) Reported in part in Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964, p. 27D.

(2) To whom inquiries should be addressed.

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(5) M. L. Wolfrom, H. El Khadem, and H. Alfes, *J. Org. Chem.*, **29**, 2072 (1964).

(6) M. L. Wolfrom, G. F. Fraenkel, D. R. Lineback, and F. Komitsky, Jr., *ibid.*, **29**, 457 (1964).

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