As may be seen from Table III, the calculations of the percentage HEAH for some ten proteins shows a variation in the percentage HEAH from less than 10% for γ-globulin to 60% for insulin. It can be concluded from these data that, on the one hand, γ-globulin contains a very small amount of strongly-hydrogen-bonded amide groups whereas insulin has more than one-half of its amide groups strongly hydrogen-bonded or in hydrophobic regions. As indicated in the table the average deviation for a series of measurements is slightly less than ±5%.

TABLE III

Protein	Approx. *p*D[a]	% HEAH[b] (10 min.)	Av. dev., %	Number of detn.	% HEAH (24 hr.)
Insulin	2	60	±2	3	12
Ovalbumin	5	50	±4	4	20
Lysozyme	4.5–5	45	±5	4	15
Chymotrypsin	4.5	43	±7	4	15
Bovine plasma albumin	5	40	±4	3	<5
Ribonuclease	4.5	35	±6	4	12
β-Lactoglobulin	5–5.5	25	±5	3	10
Chymotrypsinogen	4	20	±6	3	10
Trypsin	4	14	±4	3	5
γ-Globulin	4	<10		4	<10

[a] The *p*D's were measured using narrow range indicator paper. It is possible that the rate of deuterium exchange in proteins is highly *p*D dependent, even where no change of conformation occurs. We have tried to make all the determinations between *p*D 4 and 5, except in the case of insulin which is not soluble at this *p*D. [b] From the data given by Linderstrøm-Lang, *et al.*,[4] we have calculated the percentage HEAH they found at the beginning of deuterium exchange (using another method) to have been: insulin, 66; ribonuclease, 45.

If we compare the data in Table III with estimates of the excess right-handed helical contents obtained for the same proteins by optical rotatory dispersion,[17] we note that in general the infrared–deuterium exchange method shows higher values. A somewhat better agreement is shown between the deuterium exchange data and the estimates obtained from rotation measurements at the sodium D line.[18] At this time we offer little in the way of definitive explanations for the differences observed between the results obtained with optical rotation and those with deuterium exchange. With the infrared technique described herein we do not make the tacit assumption that the "hard-to-exchange amide hydrogens" necessarily represent the helical conformation of polypeptides and proteins, although we use a helical polypeptide as a model for a substance containing "hard-to-exchange amide hydrogens." The low values obtained with rotatory dispersion measurements may be caused by the fact that this method measures only the excess of one sense of helix over the other sense of helix and polypeptide chains with both sense of helix may exist in proteins. Alternative explanations of these data are that in proteins in addition to the hard-to-exchange amide hydrogens associated with helical portions of the polypeptide chains there are other regions of hard-to-exchange amide hydrogens. These may lie in β-structures or in areas of the polypeptide chain so surrounded by hydrophobic bonds that the deuterium exchange reaction is very slow.

Acknowledgment.—We wish to thank Dr. D. B. Wetlaufer and D. T. Miyazawa for many interesting discussions.

(17) P. Doty, *Rev. Mod. Phys.*, **31**, no. 1, 107 (1959).

(18) C. Schellman and J. A. Schellman, *Compt. rend. Lab. Carlsberg, ser. chim.*, **30** (26), 463 (1958).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE, MENLO PARK, CALIFORNIA]

Potential Anticancer Agents.[1] LIV. Synthesis of 3-Amino-2,3-dideoxy-β-D-ribofuranosides *via* the 2,3-Episulfonium Ion Approach

BY CHARLES D. ANDERSON,[2] WILLIAM W. LEE, LEON GOODMAN AND B. R. BAKER

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Application of a synthetic sequence involving migration of an ethylthio group *via* an episulfonium intermediate led to a synthesis of 3-amino-2,3-dideoxy-D-ribose isolated as its hydrochloride XVII. The 3-ethylthio glycoside I was converted to its 5-O-trityl derivative V, then treated with methanesulfonyl chloride to give the chloroglycoside VIII. Azidolysis of the chloro compound VIII gave the mixture of azides IX which was reduced to the amine mixture XIII. Acetylation of XIII and fractional crystallization of the mixture gave both acetamidoethylthiofuranosides XI and XVI with the former, originating from opening of the episulfonium ion intermediate at C.3, as the very predominant isomer. Desulfurization of the two isomers XI and XVI gave the crystalline acetamido dideoxy isomers X and XV, whose assumed structures were shown to be correct by analysis of their proton magnetic resonance spectra. A two-step hydrolysis of X gave first the free sugar, 3-acetamido-2,3-dideoxy-D-ribose (XIV) which, in turn, was converted to the amino dideoxy sugar (XVII).

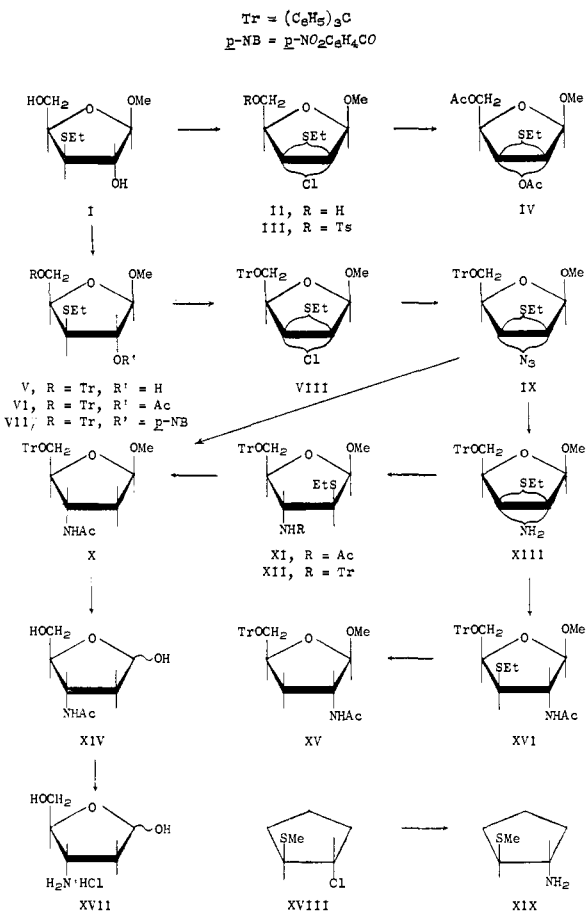
Two previous papers in this series described the synthesis of 2-deoxy-β-D-ribofuranosides[3] and of 2′-deoxyadenosine[4] both utilizing 2,3-episulfonium ions as key intermediates. These successful syntheses demonstrated the utility of this episulfonium approach for the preparation of unnatural

(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-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, *cf.* J. 1. DeGraw, L. O. Ross, L. Goodman and B. R. Baker, *J. Org. Chem.*, **26**, in press (1961).

(2) Pacific Lutheran College, Tacoma 44, Washington.

(3) C. D. Anderson, L. Goodman and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 898 (1959).

(4) C. D. Anderson, L. Goodman and B. R. Baker, *ibid.*, **81**, 3967 (1959).



2′-deoxyribose derivatives and of nucleosides containing unnatural 2′-deoxyribose moieties. This communication is concerned with the preparation of such an unnatural sugar, 3-amino-2,3-dideoxy-D-ribose hydrochloride, the accompanying paper[5] describes the application of the method to synthesis of the nucleoside, 3′-amino-2′,3′-dideoxyadenosine.

The reaction of methyl 3-deoxy-3-(ethylthio)-β-D-xylofuranoside (I)[3] with thionyl chloride at 0° afforded a high yield of a dark oil that was chromatographically homogeneous and which gave fair analytical figures for the chloroglycoside II. These were the conditions used to form the chloronucleoside that was an intermediate in the synthesis of 2′-deoxyadenosine[4] and the apparent formation of only a monochloro derivative (II) was not unexpected. The preparations of the acetate and the *p*-nitrobenzoate of II did not lead to crystalline compounds. Acetolysis of II using the conditions employed for the tosylate III[3] followed by acetylation of the product gave a good yield of the mixture of diacetates IV which showed the same gas chromatographic behavior as the product from the acetolysis of III.[3] The reaction of II with ammonia using a variety of conditions was investigated. Ammonolysis in aqueous ethanol at 100° gave some introduction of nitrogen into the product but a considerable amount of starting material was recovered. The use of ammonium carbonate in aqueous ethanol at 100° gave back much starting material, and there was no evidence for formation of an appreciable amount of amino compound. The reaction of II with potassium phthalimide in N,N-dimethylformamide (DMF) at 90° gave a product whose infrared spectrum indicated at least a partial formation of a phthalimido glycoside but no pure product could be isolated.

The resistance of II to direct ammonolysis appeared surprising, and it seemed of interest to examine the behavior of a model cyclopentyl compound in its reaction with ammonia. Accordingly *trans*-2-(methylthio)-cyclopentyl chloride (XVIII)[6] was allowed to react with ammonia in aqueous ethanol at room temperature and gave an 84% yield of the free amine (XIX). The hydrochloride and the picrate of XIX were obtained as crystalline derivatives. This large difference in reactivity between a glycoside in the furanose form and the analogous cyclopentyl compound has been noted previously[6] and is especially striking in a comparison of the reactivity of epoxides of the two types of compounds with a given nucleophile.[3,6]

In view of the lack of success in the attempted ammonolysis of II, attention was directed to a more powerful nucleophile, azide ion, as the source of introduction of a potential amine group into the furanose ring. Further, the uncertainty concerning the purity of II made it seem profitable to preferentially block the primary hydroxyl of I before proceeding to the formation of a chloroglycoside. The reaction of I with trityl chloride in pyridine at 40° gave a quantitative yield of a gum which was homogeneous according to paper chromatography and which gave fair analytical data for the monotrityl compound (V). Acetylation of V gave the 2-O-acetate VI as a gum which could not be crystallized; treatment of V with *p*-nitrobenzoyl chloride, however, yielded the crystalline *p*-nitrobenzoate VII. The strong preference for tritylation of primary as compared with secondary hydroxyls[7] favored V as the tritylation product, and this assumption was put on firmer ground by the formation of a quantitative yield of the chloro glycoside VIII as an analytically pure oil when compound V was allowed to react with methanesulfonyl chloride in pyridine.[8] The chloro glycoside VIII with sodium azide in aqueous 2-methoxyethanol gave a good yield of the oily mixture of azides IX which was characterized by the strong infrared absorption at 4.72μ. The mixture of azides IX was reduced to the mixed amines XIII by reduction with lithium aluminum hydride in ether. The amine mixture XIII was acetylated with acetic anhydride in pyridine, and the two crystalline isomeric N-acetates XI and XVI were obtained from the crude acetylation product by recrystallization. The isolated higher-melting isomer (m.p. 196–197°) constituted a 21% yield (from IX), and the lower-melting isomer (m.p.

(5) W. W. Lee, A. Benitez, C. D. Anderson, L. Goodman and B. R. Baker, *J. Am. Chem. Soc.*, **83**, 1906 (1961); Paper XLII of this series.

(6) L. Goodman, A. Benitez and B. R. Baker, *ibid.*, **80**, 1680 (1958).

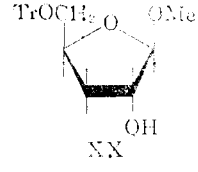
(7) B. Helferich, "Advances in Carbohydrate Chemistry," Vol. III, Academic Press, Inc., New York, N. Y., 1948, p. 79.

(8) If the reaction of I and chlorotriphenylmethane had given a 2-O-trityl compound, the further reaction with methanesulfonyl chloride would have been expected to give the 3-ethylthio-5-O-mesyl-2-O-trityl glycoside.[3]

162–164°) constituted a 1.6% yield (from IX) with the remainder of the material being a mixture of the two isomers. On a smaller scale, 46% (based on IX) of the higher-melting isomer was isolated. This was a 48% yield based on I and constituted an average yield of almost 86% per step for the 5 steps I → V → VIII → IX → product.

From the results of the acetolysis of III in which C.3 opening of the episulfonium ion was strongly favored, it was felt that the major isomer from the azidolysis of VIII would be the 3-azido-2-ethylthio isomer of IX which, in turn, would lead to the 3-acetamido isomer XI as the major product from XIII. These expectations were borne out by a study of the proton magnetic resonance spectra[9] of XI and of the desulfurization products X and XV which were obtained as crystalline solids in good yields.

The higher melting isomer of the N-acetyl compound gave proton resonance doublets centered at 293 and 197 c.p.s. with coupling constants of 4 c.p.s. as would be expected for the *cis* C.1–C.2 hydrogens of XI. The n.m.r. spectrum of the desulfurization product X showed a pair of doublets centered at 298 c.p.s. which are attributed to the C.1 hydrogen. The two doublets represent coupling of the C.1 proton to the two non-equivalent protons at C.2 with the more strongly coupled doublet (5 c.p.s.) representing coupling to the *cis*-hydrogen and the weakly coupled doublet (1 c.p.s.) representing coupling to the *trans*-hydrogen at C.2. For comparison the trityl derivative V was desulfurized to give an analytically-pure gum (XX) whose n.m.r. spectrum was determined. The C.1 hydrogen peak of XX



XX

appeared as a sharp singlet at 289 c.p.s. indicating that the hydrogen at C.1 is not detectably coupled with the *trans*-hydrogen at C.2. The spectrum of the lower-melting N-acetyl compound was in complete agreement with that predicted for structure XV. It showed a sharp singlet at 286 c.p.s. for the C.1 hydrogen which is accordingly not appreciably coupled with the *trans*-hydrogen at C.2, the situation being the same as for XX. These spectral results demonstrate the power of the n.m.r. method in differentiating between 2-deoxy- and 3-deoxy sugars.

It was interesting to note that in the Raney nickel desulfurizations of the trityl compounds V, XI and XVI, there was no evidence of appreciable hydrogenolytic loss of the trityl group. This retention of the trityl group was somewhat surprising since O-trityl and N-trityl groups have been cleaved to triphenylmethane on hydrogenation with palladium or platinum catalysts[10] under mild conditions.

A more direct route to the N-acetyl glycoside X was available by the Raney nickel treatment of the azide mixture IX in refluxing dioxane. Desulfurization and azide reduction occurred simultaneously to give a mixture of the 2(3)-amino-2,3-dideoxy-5-O-trityl glycosides. Acetylation of the mixture and recrystallization of the mixture of N-acetyl glycosides permitted the isolation of X in a yield that was comparable to that obtained by the longer route, IX→XIII→XI→X. Treatment of the mixed azides IX with Raney nickel in 2-methoxyethanol was accompanied by alkylation of the first-formed amine by the primary alcohol used as a solvent since the product, on acetylation, showed no amide-NH infrared absorption near 6.5 μ but did show amide C=O absorption at 6.02 μ. The alkylation of amines by primary or secondary alcohols in the presence of Raney nickel has considerable precedent.[11]

The amine mixture XIII was also characterized by the formation of a crystalline N-trityl derivative to which the *arabino*-configuration XII was assigned without further proof in accordance with the arguments advanced for the structure of XI.

Detritylation of the N-acetyl glycoside X with hot 80% aqueous acetic acid was accompanied by hydrolysis of the glycoside linkage to give the free acetamido sugar XIV as a widely melting crystalline compound that was analytically and chromatographically pure. The physical and chemical behavior of XIV suggested that it exists as a highly stable hemi-acetal both in solution and in the solid state.[12] The solid material showed no aldehyde C=O infrared absorption and the compound failed to give a Benedict test for a reducing sugar under conditions for which glucosamine hydrochloride and most simple sugars give a positive test. On long heating at steam-bath temperature, however, compound XIV did give a positive Benedict test. The product was also not detectable on paper chromatograms by the aniline citrate spray reagent[13] which is used for reducing sugars. Neither XIV, nor its precursor X, gave a positive test with the cysteine hydrochloride reagent[14] for 2-deoxy sugars. An aqueous solution of XIV did not mutarotate but did slowly reduce periodate, nearly one mole of this oxidant being consumed after 5 hr. The periodate behavior suggests that a small equilibrium amount of the open chain sugar XXI exists in solution. Efforts to prepare a crystalline derivative of XIV,

(9) The proton spectra were obtained with a Varian V-4300C High Resolution n.m.r. Spectrometer operating at 60 mc. Samples were studied at 25° in dilute solutions in deuterochloroform to which approximately 1% tetramethylsilane was added as an internal reference. The positions of the various peaks are expressed in c.p.s. on the low-field side of the reference peak. The authors are indebted to Drs. James N. Shoolery and Leroy F. Johnson at Varian Associates Palo Alto, California, for obtaining these data and interpreting the results.

(10) (a) P. E. Verkade, W. D. Cohen and A. K. Vroege, *Rec. trav. chim.*, **59**, 1123 (1940); (b) P. E. Verkade, F. D. Tollenaar and T. A. P. Posthumus, *ibid.*, **61**, 373 (1942); (c) F. Micheel, *Ber.*, **65**, 262 (1932); (d) L. Zervas and D. M. Theodoropoulos, *J. Am. Chem. Soc.*, **78**, 1359 (1956); (e) G. E. Stelakatos, D. M. Theodoropoulos and L. Zervas, *ibid.*, **81**, 2884 (1959).

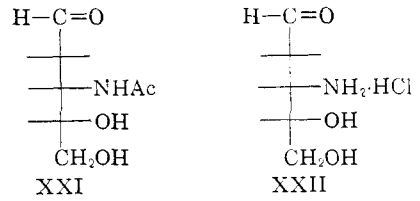
(11) *Cf.* C. Ainsworth, *J. Am. Chem. Soc.*, **78**, 1635 (1956).

(12) Structure XIV is written as the furanose form of the hemi-acetal but there is no evidence bearing on the actual ring size and the pyranose form cannot be excluded.

(13) A. A. White and W. C. Hess, *Arch. Biochem. Biophys.*, **64**, 57 (1956).

(14) Z. Dische in "The Nucleic Acids," Vol. I, ed. by E. Chargaff and J. N. Davidson, Academic Press, Inc., New York, N. Y., 1955, p. 286.

using a variety of reagents that gave good results with 2-deoxyribose, were unsuccessful.



Hydrolysis of XIV either with 4 *M* hydrochloric acid for 1 hr. or with 0.4 *M* hydrochloric acid for 22 hr. both at steam-bath temperature gave quantitative yields of a hygroscopic gum whose infrared spectrum showed no N-acetyl absorption and for which elemental analyses gave excellent agreement with the free sugar hydrochloride XVII structure. The compound gave a negative Benedict test even on warming, did not mutarotate appreciably in aqueous solution and did not respond to the ninhydrin or aniline citrate[13] reagents. Merely evaporating a methanol solution of XVII resulted in the partial formation of the methyl glycoside of XVII. This ease of glycosidation is similar to that of 2-deoxyribose.[15] The ease of hydrolysis of the glycosidic linkage of X similarly finds analogy in the chemistry of 2-deoxyribose.[15] The hydrochloride XVII consumed periodate slowly with the consumption reaching 1.6 moles after 24 hr. These data suggest that an equilibrium concentration of the open-chain sugar XXII exists in solution.

The free sugar XVII was stable to prolonged heating in aqueous hydrochloric acid, there was no evidence of change in the recovered sugar. The material was rapidly destroyed in 0.1 *M* sodium hydroxide, the solution darkening and giving off an alkaline gas, presumably ammonia. The alkaline instability of sugars with an amine group β to a carbonyl group, or a potential carbonyl group, has been noted previously.[16]

Efforts to characterize compound XVII as a crystalline solid were unsuccessful. None of the typical carbonyl derivatives were solids and attempts to convert XVII back to the N-acetyl derivative XIV did not give crystalline material, possibly because of difficulties in reestablishing the same ring structure or anomeric composition that was present in crystalline XIV.[12]

Experimental[17]

Methyl 3(2)-Chloro-2,3-dideoxy-2(3)-(ethylthio)-β-D-arabino-(xylo)-furanoside (II).—Methyl 3-deoxy-3-(ethylthio)-β-D-xylofuranoside (I) (4.80 g., 23.0 mmoles) was cooled to 0°, dissolved in 15 ml. (0.21 mole) of thionyl chloride and the solution was stirred at 0° for 30 minutes under dry nitrogen. The solution was poured into a stirred suspension of 75 g. (0.89 mole) of sodium bicarbonate, 60 ml. of chloroform and 150 ml. of water and ice. The mixture was stirred 30 minutes, diluted with 300 ml. of water and the layers separated. The aqueous phase was extracted with four 150-ml. portions of chloroform which were combined with the original chloroform layer and dried over magnesium sulfate. Evaporation of the dried extracts *in vacuo*, finally at 35° and 0.5 mm., left 4.78 g. (91%) of a dark brown oil, λ_{max}^{film} 2.92μ (OH), 7.91 μ (SEt), which moved as a single spot on paper chromatography in solvents C and D with R_{ad} 1.56 and 3.10, respectively, using spray G.

Anal. Calcd. for $C_8H_{15}ClO_3S$: C, 42.4; H, 6.67; Cl, 15.6. Found: C, 43.5; H, 6.74; Cl, 16.1.

Methyl 5,3(2)-Di-O-acetyl-2,3-dideoxy-2(3)-(ethylthio)-β-D-arabino-(xylo)-furanoside (IV).—Freshly prepared chloroglycoside II, (0.414 g., 1.80 mmole) was dissolved in 12 ml. of 95:5 2-methoxyethanol–water which contained 1.20 g. (15.0 mmoles) of anhydrous sodium acetate. The solution was heated at reflux in a nitrogen atmosphere for 3 hr. and evaporated *in vacuo*. The residue was suspended in 20 ml. of absolute ethanol and the solution evaporated *in vacuo*. The resulting residue was dissolved in 7.5 ml. of reagent pyridine, and 2.5 ml. of acetic anhydride was added to the stirred solution. After the solution had stood 48 hr. at room temperature protected from moisture, 2.0 ml. of methanol was added and the mixture was poured into 40 ml. of water. The product was extracted from the aqueous mixture with three 15-ml. portions of chloroform; the combined extracts were dried over magnesium sulfate and evaporated to dryness *in vacuo*, finally at 35° and 0.5 mm., to yield 0.451 g. (85%) of the diacetate IV. Vapor phase chromatography on a 6 ft. DC 710 column at 237° showed that both the 2-ethylthio and 3-ethylthio components of IV were present but because of poor resolution the proportions of the two components could not be determined.[3]

Evaporative distillation of 0.337 g. of the material at 90–100° (bath temperature) and 0.20 mm. afforded 0.11 g. of a nearly colorless oil with $n^{20}D$ 1.4780 and an infrared spectrum identical with that of the diacetate ($n^{20}D$ 1.4786) obtained by acetolysis of the 5-O-tosyl derivative (III).[3]

***trans*-2-(Methylthio)-cyclopentylamine (XIX).**—Concentrated aqueous ammonia (2400 ml.) was added to a solution of 118 g. (0.780 mole) of *trans*-2-(methylthio)-cyclopentyl chloride (XVIII)[6] in 1500 ml. of 95% ethanol, and the mixture was stirred in a stoppered flask at room temperature for 22 hr. The solution was made alkaline by the addition of 500 ml. of 3 *M* aqueous sodium hydroxide and extracted with five 500-ml. portions of chloroform, the combined extracts were dried over potassium carbonate and concentrated by distillation of the chloroform and ethanol through a 12″ Vigreux column at atmospheric pressure. The dark, residual liquid (102 g.) was then distilled through the same column at reduced pressure affording a colorless distillate that was collected in three fractions: (a) 2.7 g., b.p. 70–73° (9 mm.), $n^{20}D$ 1.5104; (b) 26.4 g., b.p. 73–80° (10 mm.), $n^{20}D$ 1.5140; and (c) 58.9 g., b.p. 80° (10 mm.), $n^{20}D$ 1.5144. Fractions b and c represented an 84% yield and had identical infrared spectra; $\lambda_{max(\mu)}^{film}$ 3.00, 3.08, 6.27 (NH_2). Fraction c was used for analysis.

Anal. Calcd. for $C_6H_{13}NS$: C, 54.9; H, 9.99; N, 10.7. Found: C, 55.0; H, 10.2; N, 10.4.

From an earlier experiment, the aqueous ammonolysis mixture was acidified to *p*H 1–2 with concentrated hydrochloric acid and continuously extracted with dichloromethane for 3 hr. Distillation of the dried extract afforded a residue that crystallized on cooling. The residue was trit-

(15) W. G. Overend and M. Stacey in "The Nucleic Acids," Vol. I ed. by E. Chargaff and J. N. Davidson, Academic Press, Inc., New York, N. Y., 1955, p. 9.

(16) E. H. Flynn, M. V. Sigal, Jr., P. F. Wiley and K. Gerzon, *J. Am. Chem. Soc.*, **76**, 3121 (1954).

(17) Boiling points and melting points are uncorrected. The latter were obtained with the Fisher-Johns apparatus. Optical rotations were measured with a Standard Polarimeter Model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solutions. The paper chromatograms were run by the descending technique on Schleicher and Schuell No. 2043B acetylated paper using benzene-water-methanol (2/1/6) as Solvent A[18] or on Whatman No. 1 paper in the following solvent systems: B, water; C,[19] butanol-acetic acid-water (5/2/3); D,[20] water-saturated butanol; E,[21] ethyl-acetate-pyridine-water (2/1/2). The spots were detected by visual examination under ultraviolet light or by use of the following spray reagents: F, ninhydrin; G,[22] bromine; H,[23] periodate-permanganate. Adenine was used as a standard and the spots were located relative to R_{Ad} 1.00.

(18) Th. Wieland and W. Kracht, *Angew. Chem.*, **69**, 172 (1957).

(19) D. M. Brown, A. Todd and S. Varadarajan, *J. Chem. Soc.*, 2388 (1956).

(20) J. G. Buchanan, C. A. Dekker and A. G. Long, *ibid.*, 3162 (1950).

(21) M. A. Jermyn and F. A. Isherwood, *Biochem. J.*, **44**, 402 (1949).

(22) F. Weygand, H. J. Bestmann and H. Ziemann, *Ber.*, **91**, 1040 (1958).

(23) R. U. Lemieux and H. F. Bauer, *Anal. Chem.*, **26**, 920 (1954).

rated with acetone leaving a white solid of XIX hydrochloride, m.p. 141–144°. Recrystallization from acetone–benzene gave white plates, m.p. 142–144°; $\lambda_{max(\mu)}^{KBr}$ 3.40, 6.23, 6.32, 6.54 (NH_3^+).

Anal. Calcd. for $C_6H_{13}NS\cdot HCl$: C, 43.0; H, 8.41; Cl, 21.1. Found: C, 43.0; H, 8.49; Cl(ionic), 21.0.

Treatment of a portion of *trans*-2-(methylthio)-cyclopentylamine (XIX) dissolved in ether with an ethereal solution of picric acid afforded a yellow picrate which was washed with ether and dried *in vacuo*, m.p. 151–154°; $\lambda_{max(\mu)}^{KBr}$ 3.40 (NH_3^+), 6.09, 6.16 (NH_3^+, phenyl); 6.48 (NO_2).

Anal. Calcd. for $C_{12}H_{16}N_4O_7S$: C, 40.0; H, 4.48; S, 8.88. Found: C, 40.1; H, 4.71; S, 8.59, 8.72.

The picrate appeared to decompose upon recrystallization from benzene–hexane and from acetone as shown by a large change in melting range and poor elemental analyses for the resulting product.

Methyl 3-Deoxy-3-(ethylthio)-5-O-trityl-β-D-xylofuranoside (V).—A solution of 1.04 g. (5.0 mmoles) of the ethylthio glycoside I and 1.40 g. (5.0 mmoles) of chlorotriphenylmethane in 6.0 ml. of reagent pyridine was heated at 40° for 18 hr. protected from moisture. The mixture was cooled to room temperature, diluted with 10 ml. of chloroform, poured into 30 ml. of 1 *M* aqueous sodium bicarbonate solution and stirred at room temperature for 45 minutes. The chloroform layer was separated, washed with 15 ml. of water, dried over magnesium sulfate and evaporated *in vacuo*. The residue was twice redissolved in 10-ml. portions of toluene and re-evaporated, finally at 35° and 0.5 mm. to yield 2.60 g. (112%) of a residual gum; $\lambda_{max(\mu)}^{film}$ 2.87 (OH), 6.25 and 6.67 (phenyl), 7.88 (SEt). It traveled as a single spot in solvent A with R_{Ad} varying from 0.68 to 0.85 when viewed under ultraviolet light and separating well from I and triphenylcarbinol. The analytical sample, prepared by drying crude II at 56° and 0.2 mm. for 2 hr., had $[\alpha]^{27}D$ −3° (1.0% in chloroform).

Anal. Calcd. for $C_{27}H_{30}O_4S$: C, 72.0; H, 6.71; S, 7.12. Found: C, 72.8; H, 6.81; S, 6.28.

Methyl 2-O-Acetyl-3-deoxy-3-(ethylthio)-5-O-trityl-β-D-xylofuranoside (VI).—A solution of 0.24 g. (0.50 mmole) of V in 5 ml. of pyridine was treated with 1.0 ml. (11 mmoles) of acetic anhydride and left at room temperature (protected from moisture) for 22 hr. The usual work-up of decomposing with water, partitioning into dichloromethane, drying and evaporating afforded 0.25 g. (96%) of the acetate VI as a colorless gum; $\lambda_{max(\mu)}^{film}$ 5.73 (acetate C=O); 6.26 and 6.79 (phenyl), 7.91 (SEt), 8.16 (acetate C–O–C). The analytical sample, dried at 56° and 0.2 mm. for 1 hr., had $[\alpha]^{23}D$ −27° (1.2% in chloroform).

Anal. Calcd. for $C_{29}H_{32}O_5S$: C, 70.7; H, 6.55; S, 6.49. Found: C, 70.7; H, 6.72; S, 6.61.

Methyl 3-Deoxy-3-(ethylthio)-2-O-(*p*-nitrobenzoyl)-5-O-trityl-β-D-xylofuranoside (VII).—A solution of 1.92 g. (4.2 mmoles) of the trityl ether V in 12 ml. of reagent pyridine was cooled to 0°, 1.56 g. (8.4 mmoles) of *p*-nitrobenzoyl chloride was added and the mixture was stirred at 0° for 0.5 hr. (protected from moisture), then at room temperature for 70 hr. Water (0.4 ml.) was added and, after being stirred for 1 hr., the mixture was diluted with 60 ml. of chloroform, washed with three 20-ml. portions of 1 *M* aqueous sodium bicarbonate, with two 20-ml. portions of water, dried over magnesium sulfate and evaporated *in vacuo*. The residue was dissolved in 15 ml. of toluene and re-evaporated, finally at 40° and 0.5 mm., to afford 2.11 g. of a gum. Crystallization of the residue from heptane yielded 1.48 g. of crystalline VII, m.p. 163–170°. Recrystallization from 20:1 heptane–ethyl acetate afforded 1.11. g. (44%) of crystalline solid, m.p. 175–176°; $\lambda_{max(\mu)}^{Nujol}$ 5.75 (ester C=O), 6.23 (phenyl), 6.53 (NO_2); $[\alpha]^{24}D$ 10° (1.0% in chloroform).

Anal. Calcd. for $C_{34}H_{33}NO_7S$: C, 68.1; H, 5.55; S, 5.35. Found: C, 68.3; H, 5.62; S, 5.35.

Methyl 3(2)-Chloro-2,3-dideoxy-2(3)-(ethylthio)-5-O-trityl-β-D-arabino-(xylo)-furanoside (VIII).—A solution of 1.00 g. (2.20 mmoles) of trityl ether V in 10 ml. of reagent pyridine was cooled to 0° and treated with 0.40 ml. (5.2 mmoles) of methanesulfonyl chloride. The mixture (protected from moisture) was then left at room temperature for 64 hr., after which 0.1 ml. of water was added to the stirred solution. After 2.5 hr. at room temperature, the mixture was poured into 50 ml. of water and extracted with two 20-ml. portions of chloroform. The combined extracts were dried over magnesium sulfate and evaporated *in vacuo*. The residue was dissolved in 20 ml. of toluene and re-evaporated, finally at 35° and 0.5 mm., to leave 1.02 g. (98%) of an oil; $\lambda_{max(\mu)}^{film}$ 6.25, 6.78 and 6.89 (phenyl), 7.89 (SEt); there was essentially no hydroxyl absorption near 3.0. The analytical sample was prepared by drying at 56° and 0.2 mm. for 1.5 hr. and had $[\alpha]^{27}D$ −11° (1.0% in chloroform).

Anal. Calcd. for $C_{27}H_{29}ClO_3S$: C, 69.1; H, 6.23; Cl, 7.60. Found: C, 70.2; H, 6.28; Cl, 7.41, 7.79.

On a large scale 258 g. of the trityl ether V afforded 257 g. of the chloroglycoside VIII.

Methyl 3(2)-Azido-2,3-dideoxy-2(3)-(ethylthio)-5-O-trityl-β-D-arabino-(xylo)-furanoside (IX).—A stirred solution of 0.82 g. (1.70 mmole) of the chloro glycoside VIII and 0.98 g. (15 mmoles) of sodium azide in 10 ml. of 95:5 2-methoxyethanol–water was heated at reflux under nitrogen for 3 hr. The cooled mixture was then evaporated to dryness *in vacuo*, and the residue was partitioned between 40 ml. of water and 25 ml. of chloroform. The aqueous phase was further extracted with two 10-ml. portions of chloroform. The combined chloroform extracts were washed with 15 ml. of saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated to dryness *in vacuo*. The residue was dissolved in 15 ml. of toluene and re-evaporated, finally at 35° and 0.5 mm., to leave 0.77 g. (93%) of an oil; $\lambda_{max(\mu)}^{film}$ 4.72 (N_3); 6.24, 6.67 and 6.88 (phenyl), 7.88 (SEt).

On a large scale 257 g. of the chloro glycoside VIII gave 229 g. (88%) of the azido compound IX.

When the chloro glycoside II was treated under the same conditions as above, the product, obtained in about 60% yield, was an oil which showed strong infrared absorption at 4.75 μ but which analyzed for only 71% of the theoretical nitrogen.

Methyl 3(2)-Amino-2,3-dideoxy-2(3)-(ethylthio)-5-O-trityl-β-D-arabino-(xylo)-furanoside (XIII).—A solution of 0.57 g. (1.2 mmoles) of the crude mixture of azide glycosides IX in 10 ml. of dry ether was added dropwise over a period of 10 minutes to a stirred suspension of 0.11 g. (3.0 mmoles) of lithium aluminum hydride in 20 ml. of dry ether while taking the usual precautions against atmospheric moisture. The mixture then was heated at reflux for 1.5 hr. and the excess hydride destroyed by the dropwise addition of 3 ml. of absolute ethanol. Fifteen ml. of 10% aqueous sodium hydroxide solution was added and the mixture was stirred until the originally gray solids were pure white. The organic phase was decanted and the aqueous phase was washed by the addition and decantation of three 10-ml. portions of benzene, care being taken to avoid emulsions. The aqueous phase was then diluted with an additional 10 ml. of 10% aqueous sodium hydroxide and filtered through Celite using suction. The solid residue was washed with two 10-ml. portions of 10% aqueous sodium hydroxide and two 10-ml. portions of benzene. The organic layer of the filtrate was separated and the aqueous phase was further extracted with two 10-ml. portions of benzene. The combined benzene extracts together with the original ether layer were dried over magnesium sulfate and evaporated *in vacuo*, finally at 40° and 0.5 mm., to yield 0.45 g. (83%) of a gum, $\lambda_{max(\mu)}^{film}$ 2.98 (NH_2), 6.16–6.24 (NH_2 and phenyl), 6.67 and 6.88 (phenyl), 7.88 (SEt), which traveled as a single spot in solvent A with R_{Ad} 0.59 when viewed under ultraviolet light.

Methyl 3-Acetamido-2,3-dideoxy-2-(ethylthio)-5-O-trityl-β-D-arabinofuranoside (XI) and Methyl 2-Acetamido-2,3-dideoxy-3-(ethylthio)-5-O-trityl-β-D-xylofuranoside (XVI).—A stirred solution of 2.43 g. (5.30 mmoles) of crude amino glycoside (XIII) in 20 ml. of reagent pyridine cooled to 0° was treated with 1.00 ml. (10.6 mmoles) of acetic anhydride. After the solution had stood at room temperature for 18 hr., protected from moisture, it was poured slowly and with rapid stirring into 150 ml. of 0.3 *M* aqueous sodium bicarbonate. The oil that separated was collected by extraction with three 20-ml. portions of chloroform. The combined extracts, dried over magnesium sulfate, were evaporated *in vacuo*. The residue was dissolved in 15 ml. of toluene and re-evaporated *in vacuo*, finally at 35° and 0.5 mm., to afford 2.53 g. (96%) of a stiff gum. Crystallization of 2.40 g. of this gum from heptane–ethyl acetate yielded two crops of crystalline XI: (a) 0.79 g., m.p. 190–193°, and (b) 0.66 g., m.p. 182–192°, for a total yield of 58%. Recrystallization of (a) from heptane–ethyl acetate gave 0.47 g. of white needles, m.p. 194–196°, unchanged by further recrystallization;

$\lambda_{max(\mu)}^{Nujol}$ 3.00 and 6.45 (NH); 6.04 (amide C=O); 6.25 and 6.68 (phenyl), 7.97 (SEt); $[\alpha]^{26}D$ −44° (1.0% in chloroform). It moved as a single spot in solvent A with R_{Ad} 1.00 when viewed under ultraviolet light.

Anal. Calcd. for $C_{29}H_{33}NO_4S$: C, 70.9; 6.77; N, 2.85. Found: C, 71.1; H, 6.80; N, 2.83.

In a large-scale run 229 g. of azido glycoside IX was reduced with lithium aluminum hydride and the product directly acetylated as above to give 215 g. (91%) of a mixture of XI and XVI. Three crystallizations, first from an ethyl acetate–Skellysolve C (b.p. 88–99°) mixture and twice from ethyl acetate, yielded 49 g. (21%) of XI, m.p. 196–197°, which agreed well by paper chromatographic and infrared comparison with the analytical sample.

The mother liquors from the second crystallization of XI (m.p. 190–193°) were evaporated to a volume of *ca.* 100 ml. *in vacuo* and chilled to yield 18.6 g. of solid, m.p. 156–158°. Three recrystallizations, first from benzene–Skellysolve C, then from carbon tetrachloride–chloroform and finally from ethyl acetate, yielded 3.7 g. (1.6%) of XVI, m.p. 162–164°; $\lambda_{max(\mu)}^{Nujol}$ 3.04 and 6.41 (NH), 6.02 (amide C=O), 6.25 and 6.68 (phenyl), 7.89 (SEt); $[\alpha]^{25}D$ −14.8° (1.0% in chloroform). On paper chromatography in solvent A the compound moved as a single spot with R_{Ad} 1.00 when viewed under ultraviolet light.

Anal. Calcd. for $C_{29}H_{33}NO_4S$: C, 70.9; H, 6.77; N, 2.85. Found: C, 71.2; H, 6.97; N, 3.24, 2.84.

Methyl 3-Acetamido-2,3-dideoxy-5-O-trityl-β-D-ribofuranoside (X). A. **From the N-Acetyl Glycoside (XI).**—Raney alloy (30 g.) was converted to the catalyst "C" of Hurd and Rudner.[24] After two absolute ethanol washes and two washes with 2-methoxyethanol, the catalyst was used immediately. To the catalyst was added a solution of 1.55 g. (3.10 mmoles) of the N-acetyl glycoside XI in 150 ml. of 2-methoxyethanol and the stirred mixture was heated under reflux for 6 hr. Then 50 ml. of 95% ethanol was added and the mixture was filtered through Celite. The Celite and catalyst were washed with three 25-ml. portions of boiling 95% ethanol and the filtrate and washings were evaporated to dryness *in vacuo*. The residue was dissolved in 35 ml. of absolute ethanol and re-evaporated, finally at 35° and 0.5 mm., to yield 2.47 g. of a gum. The gum was extracted with two 50-ml. portions of boiling chloroform and the extracts, filtered while hot, were combined and evaporated *in vacuo*. The partially crystalline residue (1.44 g.) was recrystallized from ethyl acetate adding heptane to the hot solution to turbidity. The white, crystalline product (0.76 g.) had m.p. 158–161° and a second crop (0.32 g., m.p. 152–158°) brought the total yield to 82%. Recrystallization of 0.67 g. of the first crop from ethyl acetate–heptane afforded 0.66 g. of product, m.p. 160–162°; $\lambda_{max(\mu)}^{Nujol}$ 3.09 and 6.40 (NH); 6.03 (amide C=O); no band near 7.9 (EtS); $[\alpha]^{25}D$ −36° (1% in chloroform). On paper chromatography in solvent A, the compound moved as a single spot with R_{Ad} 1.2 when viewed under ultraviolet light.

Anal. Calcd. for $C_{27}H_{29}NO_4$: C, 75.2; H, 6.77; N, 3.25. Found: C, 75.3; H, 6.96; N, 3.21.

When the desulfurization of 1.50 g. of XI was carried out using 15 g. of commercial Raney nickel catalyst[25] in 150 ml. of dry dioxane with a workup similar to that described above, there was recovered 1.11 g. (83%) of X, recovered in two crops, m.p. 159–162° and 155–158°.

B. **From the Azido Glycosides (IX).**—A stirred solution of 0.68 g. (1.43 mmoles) of crude azido glycoside IX in 68 ml. of dry dioxane containing 6.8 g. of Davison nickel catalyst[25] (washed three times with dry dioxane) was heated at 75°, while protected from moisture, for 3 hr. and then at reflux for 3 hr. The mixture was worked up by the procedure used in the preparation of X to afford 0.50 g. (91%) of a sirup that had $\lambda_{max(\mu)}^{film}$ 2.96 (NH_2), 6.23 (NH_2 and phenyl), 6.66 and 6.86 (phenyl), no absorption near 4.7 (N_3) or near 7.9 (SEt). The sirup (0.46 g.) was acetylated by the procedure used to prepare XI and XVI, to yield 0.44 g. (86%) of a viscous gum. A portion of the gum, 0.41 g., was crystallized from ethyl acetate–heptane to afford two crops of crystalline X: (a) 0.050 g., m.p. 149–157°, and (b) 0.033 g., m.p. 150–159°, for a yield of 16% based on IX. These crops were combined and recrystallized from ethyl acetate–heptane to give two crops of X: (a) 0.057 g., m.p. and mixed m.p. with the analytical sample of X, 159–161°; and (b) 0.010 g., m.p. 154–157°.

Methyl 2-Acetamido-2,3-dideoxy-5-O-trityl-β-D-ribofuranoside (XV).—The desulfurization procedure for XVI followed that used in the conversion of XI to X except that 26 g. of Raney alloy was used to prepare the catalyst for desulfurization of 2.0 g. (4.0 mmoles) of the ethylthio glycoside XVI. The crude desulfurization product, 1.96 g. (111%), m.p. 70–125°, was recrystallized from 10 ml. of acetone and 20 ml. of Skellysolve B (b.p. 62–70°) to give 0.88 g. (50%) of crystalline solid, m.p. 140–145°, with resolidification and remelting at 173–174°; $\lambda_{max(\mu)}^{Nujol}$ 3.10 and 6.39 (NH), 6.08 (amide C=O), no band near 7.9 (EtS); $[\alpha]^{25}D$ −19.0° (1% in chloroform). A mixture of XV and X began to melt at 132°. On paper chromatography in solvent A, compound XV moved as a single spot with R_{Ad} 1.2 when viewed under ultraviolet light.

Anal. Calcd. for $C_{27}H_{29}NO_4$: C, 75.2; H, 6.77; N, 3.25. Found: C, 75.0; H, 6.84; N, 3.24.

Methyl 3-Deoxy-5-O-trityl-β-D-ribofuranoside (XX).—A stirred solution of 2.00 g. (4.30 mmoles) of the ethylthio glycoside V in 200 ml. of 2-methoxyethanol containing 20 g. of commercial Raney nickel catalyst[25] was refluxed for 5 hr. and processed by the procedure described for the preparation of X. The crude product was redissolved in 50 ml. of toluene, the solution filtered through Celite and the filtrate evaporated *in vacuo*, finally at 35° and 0.5 mm., to yield 1.88 g. (108%) of a colorless sirup; $\lambda_{max(\mu)}^{film}$ 2.92 (OH), 6.24, 6.68, 6.89 (phenyl), no absorption near 7.9 (SEt). On paper chromatography in solvent A, the product moved as a single spot with R_{Ad} 0.63, indistinguishable from V, when viewed under ultraviolet light. The analytical sample, $[\alpha]^{26}D$ −23° (1% in chloroform), was prepared by drying at 56° and 0.2 mm. for 16 hr.

Anal. Calcd. for $C_{25}H_{26}O_4$: C, 76.9; H, 6.71. Found: C, 76.9; H, 6.99.

Methyl 2,3-Dideoxy-2-(ethylthio)-3-(tritylamino)-5-O-trityl-β-D-arabinofuranoside (XII).—A solution of 1.01 g. (2.20 mmoles) of the amino glycoside mixture XIII, 0.66 ml. (4.8 mmoles) of triethylamine and 0.67 g. (2.4 mmoles) of chlorotriphenylmethane in 10 ml. of dichloromethane, protected from moisture, was left at room temperature for 21 hr. The solution was then washed with two 10-ml. portions of water, dried over magnesium sulfate and evaporated *in vacuo*, finally at 35° and 0.5 mm., to yield 1.46 g. (96%) of a gum. Recrystallization from 60 ml. of boiling methanol afforded 0.61 g. (40%) of white crystals, m.p. 195–201°, and two more recrystallizations from ethyl acetate yielded 0.41 g. (27%) of the analytical sample, m.p. 205–206°; $\lambda_{max(\mu)}^{Nujol}$ 6.25, 6.69, 13.06, 13.27 (phenyl), 7.91 (SEt), $[\alpha]^{25}D$ −117° (1% in chloroform). On paper chromatography in solvent A the compound moved as a single spot with R_{Ad} 0.19 when viewed under ultraviolet light.

Anal. Calcd. for $C_{46}H_{45}NO_3S$: C, 79.9; H, 6.56; S, 4.62. Found: C, 80.1; H, 6.75; S, 4.67.

3-Acetamido-2,3-dideoxy-D-ribose (XIV).—To 40 ml. of 80% aqueous acetic acid (preheated on the steam-bath) was added 1.41 g. (3.30 mmoles) of the acetamidodideoxy glycoside X and the mixture was heated on the steam-bath for 20 minutes with occasional stirring. The mixture was poured into 240 ml. of water and filtered to remove the precipitated triphenylcarbinol. The filtrate was extracted with three 100-ml. portions of hot heptane and was then evaporated to dryness *in vacuo*. The colorless residue was twice re-evaporated from absolute ethanol, finally at 35° and 0.5 mm., yielding 0.65 g. (106%) of a colorless gum. A portion of the gum (0.55 g.) was crystallized from 35 ml. of ethyl acetate, yielding 0.32 g. (61%) of white crystals, m.p. 113–115°. A recrystallization from ethyl acetate–ethanol gave 0.15 g. of white solid, m.p. 116–120°, and a second recrystallization from ethyl acetate afforded 0.10 g. of the analytical sample, m.p. 115–129°; $\lambda_{max(\mu)}^{Nujol}$ 2.91, 2.99 (OH, NH), 6.02 (amide C=O), 6.44 (amide NH); $[\alpha]^{26}D$ −77° (0.9% in water), constant over a 24-hr. period. The compound was homogeneous on paper chromatography in solvents B, C and E with R_{Ad} 2.60, 0.89 and 1.17, respectively, when detected with spray H.

Anal. Calcd. for $C_7H_{13}NO_4$: C, 48.0; H, 7.48; N, 8.00; OMe, 0. Found: C, 48.4; H, 7.68; N, 7.92; OMe, 0.

(24) C. D. Hurd and B. Rudner, *J. Am. Chem. Soc.*, **73**, 5157 (1951).

(25) Sponge nickel catalyst, Davison Chemical Co., Cincinnati 29, Ohio.

Compound XIV gave a positive Benedict test only after heating on the steam-bath but did give a positive test with Tollens' reagent. Attempts were made to derivatize XIV with *p*-nitrophenylhydrazine, methylphenylhydrazine, *p*-toluenesulfonylhydrazine, aniline and *p*-nitrobenzoyl chloride but in none of the cases could solid derivatives be obtained under conditions where 2-deoxyribose gave crystalline products readily with *p*-toluenesulfonylhydrazine and aniline.

A quantitative periodate oxidation at *p*H 5 and 27–30° temperature, followed spectrophotometrically by observation of the optical density at 310 mμ[26] showed the following consumption of equivalents of periodate ion per mole of XIV as a function of time: 15 min., 0; 30 min., 0.10; 5.0 hr., 0.85. Titration with periodate under the same conditions as the spectrophotometric determination showed the consumption of 0.5 equivalent per mole of XIV at 4 hr. and 1.0 equivalent/mole at 24 hr.

2-Amino-2,3-dideoxy-D-ribose Hydrochloride (XVII).—A solution of 2.50 g. (14.3 mmoles) of crystalline XIV in 100 ml. of 4 *M* hydrochloric acid was heated at 100° for 1 hr., then cooled and evaporated *in vacuo*, finally at 1 mm., with a maximum bath temperature of 40°. Water (5–10 ml.) was added to the residue and the solution was re-evaporated *in vacuo*. After five such treatments with water, benzene (5 ml.) was added to the residue and evaporated *in vacuo*. The benzene treatment was repeated *twice* more to leave 2.67 g. (110%) of a very hygroscopic gum which gave a very diffuse infrared spectrum when run as a film or mulled in Nujol but did show the presence of amine hydrochloride as a broad band near 3.4 μ and a sharper band at 4.86 μ; there was no amide carbonyl absorption near 6.0 μ. The gum was homogeneous on paper in solvents C and E with R_{Ad} of 0.99 and 0.71, respectively, when detected by spray H, easily distinguished from XIV. For analysis a portion of the gum was dried at room temperature over phosphorus pentoxide at 0.5 mm. and had $[\alpha]^{29}D$ −48° (1.77% in water). The rotation was unchanged after 1 hr. but had changed somewhat ($[\alpha]^{25}D$ −44°) after 89 hr.

Anal. Calcd. for $C_5H_{11}NO_3 \cdot HCl$: C, 35.4; H, 7.13; N, 8.26; Cl, 20.9. Found: C, 35.6; H, 7.30; N, 8.11; Cl, 21.2.

Compound XVII gave a positive test with Fehling's solution after warming and appeared to reduce Tollens' solution, although the test was obscured by the silver chloride formed. It did not give a positive Benedict test even on warming. Attempts to prepare a solid derivative from XVII with picric acid, *p*-nitrophenylhydrazine, *p*-toluenesulfonyl chloride or acetic anhydride were unsuccessful.

Compound XVII was stable to heating in 4 *M* hydrochloric acid at steam-bath temperatures for at least 5 hr., the material being recovered unchanged from such treatment. A solution of XVII in 1 *M* aqueous sodium hydroxide, however, darkened within a few minutes at steam-bath temperature and produced a gas that gave an alkaline reaction with moist litmus paper. Similar treatment in 0.1 *M* sodium hydroxide required about 10 minutes for noticeable decomposition. Even at room temperature in 0.8 *M* sodium hydroxide, decomposition was noticeable after about 1 hr.

Titration with periodate ion at *p*H 5 and 27–30° showed the following consumption of equivalents of oxidant per mole of XVII: 30 min., 0.9; 4 hr., 1.3; 24 hr., 1.6.

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[CONTRIBUTION FROM STANFORD RESEARCH INSTITUTE, MENLO PARK, CALIFORNIA]

Potential Anticancer Agents.[1] LV. Synthesis of 3′-Amino-2′,3′-dideoxyadenosine and Related Analogs

BY WILLIAM W. LEE, ALLEN BENITEZ, CHARLES D. ANDERSON, LEON GOODMAN AND B. R. BAKER

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The general chemical approach to deoxyribonucleosides by which 2′-deoxyadenosine was previously prepared has now been used to synthesize 3′- and 2′-aminodideoxyadenosine (VIII and IX, respectively) in two steps from the chloro ethylthio nucleoside I. Reaction of I with sodium azide afforded the two isomeric azido nucleosides IV and V, which were separable. Simultaneous reduction and desulfurization of IV and V gave VIII and IX, respectively. 3′-Deoxyadenosine (III) was also synthesized by desulfurization of the ethylthio nucleoside II.

Since the natural 2′-deoxyribonucleosides or their phosphates are the monomeric units of the DNA polymer, the synthesis of antimetabolites of these 2′-deoxynucleosides has been of major interest to workers in the cancer field. For example, antagonists composed of natural 2-deoxyribofuranose and such fraudulent bases as 6-azathymine,[3] 5-iodouracil[4] or 5-fluorouracil[5] have been shown to have anticancer activity. A relatively unexplored class of potential antagonists in the 2′-deoxynucleoside area are those that contain a fraudulent sugar moiety and a natural base. The fact that 6-dimethylamino-9-(3′-amino-3′-deoxy-β-D-ribofuranosyl)-purine, an analog of adenosine, has antitumor activity,[6] suggested that a corresponding analog of 2′-deoxyadenosine, namely, 3′-amino-2′,3′-dideoxyadenosine (VIII), should be synthesized and evaluated as an anticancer agent.

The first reported[7] synthesis of natural 2′-deoxyadenosine, which originated in this Laboratory, was deliberately designed to have the widest possible application for the synthesis of antimetabolites related to 2′-deoxyadenosine, rather than to be the most useful synthesis of a readily isolated and commercially available natural prod-

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