satisfactorily, however, it underwent partial rearrangement to the corresponding urethan as indicated by the appearance of a shoulder in the infrared spectrum at 5.92 μ. The analytical data reflect the presence of the rearranged product in the sample. The rearranged product isolated in pure form is described below.

Anal. Calcd. for $C_{12}H_{22}Cl_2N_2O_3S$: C, 41.74; H, 6.42; N, 8.11. Found: C, 40.80; H, 6.61; N, 7.86.

N,N-Bis(2-chloroethyl)carbamoyl-L-phenylalanine Ethyl Ester—This compound was prepared in 80% yield by an analogous procedure from L-phenylalanine ethyl ester isocyanate[5] giving a colorless oil, $[\alpha]^{22}D$ −17.7 (ethanol), $n^{23}D$ 1.5248.

Anal. Calcd. for $C_{16}H_{22}Cl_2N_2O_3$: C, 53.19; H, 6.14; N, 7.75. Found: C, 52.96; H, 6.03; N, 7.42.

N,N-Bis(2-chloroethyl)carbamoyl-L-leucine Ethyl Ester.—Following the procedure described above, 19 g. (0.087 mole) of L-leucine ethyl ester isocyanate[5] on condensation with bis(2-chloroethyl)amine gave a white semisolid product which was dissolved in anhydrous ether and allowed to stand for 60 hr. in the refrigerator. The product precipitated in two forms, a fine white powder and large crystals, which were filtered and separated mechanically, melting points 90–91° and 57–58°, recrystallized from ether at room temperature and at acetone–Dry Ice temperature, respectively. Yields were 3 g. (12%) and 16 g. (70%), $[\alpha]^{30}D$ 0 and −13.71°, respectively. The two had identical infrared spectra and were identified as the racemic form, m.p. 91°, and the L- form, m.p. 58°.

Anal. Calcd. for $C_{13}H_{24}Cl_2N_2O_3$ (for the racemic form): C, 47.71; H, 7.39; N, 8.56. Found: C, 47.73; H, 7.63; N, 8.82. Found (for the L- form): C, 47.63; H, 7.36; N, 8.75.

N-[2-(2′-Chloroethylamino)ethoxycarbonylleucine Hydrochloride (VII).—L-Leucine benzyl ester *p*-toluenesulfonate (Cyclo Chemical) was converted to the hydrochloride and subsequently to L-leucine benzyl ester isocyanate, b.p. 115° (0.25 mm.), by the method of Goldschmidt and Wick.[5] The isocyanate was converted to N,N-bis(2-chloroethyl)carbamoyl-L-leucine benzyl ester (VI) by condensation with bis(2-chloroethyl)amine. The benzyl ester VI (0.39 g., 0.001 mole) was dissolved in ethanol and hydrogenated catalytically using 10% Pd on charcoal as a catalyst. Rapid uptake of 1 equiv. of hydrogen resulted, after which no further reaction was observed. The solution was filtered to remove the catalyst, and water (1 ml.) was added to the filtrate to complete the rearrangement. Removal of solvent left 0.28 g. (90%) of colorless crystals, m.p. 118–119°.

Anal. Calcd. for $C_{11}H_{22}Cl_2N_2O_4$: C, 41.6; H, 7.0; Cl, 22.4; N, 8.8. Found: C, 41.5; H, 7.1; Cl, 22.1; N, 8.9.

Rearrangement of N,N-Bis(2-chloroethyl)carbamoyl-L-glutamic Acid Diethyl Ester.—A suspension of 10 g. of N,N-bis(2-chloroethyl)carbamoyl-L-glutamic acid diethyl ester in 50 ml. of water was stirred for 15 hr. at room temperature, and extracted with ether to remove any unreacted material. The ether extracts were discarded. The solvent was removed from the aqueous solution by distillation under reduced pressure at room temperature leaving a quantitative yield of the rearranged product, N-[2-(2′-chloroethylamino)ethoxycarbonyl]-L-glutamic acid diethyl ester hydrochloride as a colorless oil, $[\alpha]^{30}D$ −13.4, $n^{22}D$ 1.4929.

Anal. Calcd. for $C_{14}H_{26}Cl_2N_2O_6$: C, 43.19; H, 6.73; N, 7.19.; Found: C, 43.19; H, 6.73; N, 7.30.

N[2-(2-Chloroethylamino)ethoxycarbonyl]-L-methionine Ethyl Ester Hydrochloride.—This compound was obtained by the same procedure used above from N,N-bis(2-chloroethyl)carbamoyl-L-methionine ethyl ester. The product was a colorless oil, $[\alpha]^{31}D$ −20.1, $n^{22}D$ 1.5236.

Anal. Calcd. for $C_{12}H_{24}Cl_2N_2O_4S$: C, 39.61; H, 6.65; N, 7.71. Found: C, 39.93; H, 6.81; N, 7.80.

The Preparation of Nucleosides from Allose, Altrose, Gulose, Talose, and Mannose[1]

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New hexopyranosyl nucleosides have been synthesized from D-mannose, D-talose, D-gulose, D-allose, and D-altrose. Acetylhalogenosyl derivatives of these carbohydrates were coupled with chloromercuri-6-benzamidopurine to produce 9-α-D-mannopyranosyladenine, 9-α-D-talopyranosyladenine, 9-β-D-gulopyranosyladenine, 9-β-D-allopyranosyladenine, and 9-α-D-altropyranosyladenine, respectively. The compounds exhibited no activity against a number of microorganisms.

Many nucleosides have been synthesized in recent years in which the sugar moiety has been altered in some way in the hope of developing substances that would be useful as antitumor and/or antimicrobial agents. The basis of much of this work arose with the discovery of a number of antibiotic substances which have the basic nucleoside structure but which differ primarily in the structure of the sugar moiety. Many of the nucleoside analogs which have been synthesized have had changes made in the carbohydrate portion of the molecule, often consisting of the substitution of another functional group for a hydroxyl, or the substitution of a hydrogen to form a deoxynucleoside. Among the hexoses, only D-glucose and D-galactose have been extensively utilized without alteration. In one case, D-mannose was used with adenine to prepare a nucleoside of β-configuration.[2] Nowhere in the literature are there described the synthesis and the properties of the complete list of possible aldohexopyranosyl nucleosides in which the only difference in structure would be in the configuration at one or more of the hydroxyl groups. Knowledge of the chemical and biological properties of such a series of nucleosides derived from pentose sugars is available. It was therefore decided that nucleosides derived from the rare hexoses, D-allose, D-gulose, D-talose, and D-altrose, be synthesized and their properties studied. In addition, the previously unknown 9-α-D-mannopyranosyladenine was synthesized. Work is in progress leading to the preparation of an adenine nucleoside from the more difficultly obtainable D-idose.

Except for minor variations the same synthetic pathway was used with all of the carbohydrates. Crystalline D-mannose, D-talose, D-allose, and D-altrose were acetylated with the acetic anhydride–acetic acid reagent described by Montgomery and Hudson[3] as an

(1) (a) Abstracted from the Ph.D. thesis of L. M. Lerner; (b) supported in part by Grant P-161 from the American Cancer Society and by Training Grant No. GM-471 from the Division of General Medical Sciences of the U. S. Public Health Service.

(2) B. Lythgoe, H. Smith, and A. R. Todd, *J. Chem. Soc.*, 355 (1947).

(3) E. Montgomery and C. S. Hudson, *J. Am. Chem. Soc.*, **56**, 2463 (1934).

isomerization reagent to form α-pentaacetates. Crystalline penta-*O*-acetylallose was obtained but apparently as the β-anomer rather than the α-anomer as expected. Elementary analysis and the infrared spectrum confirmed the identity of the product as a pentaacetate, but the melting point and the optical rotation were close to those reported by Lemieux and Brice[4] for the β-anomer which they prepared using acetic anhydride with sodium acetate as a catalyst. α-D-Mannose pentaacetate was also isolated as a pure crystalline material, and the pentaacetates of altrose and talose crystallized readily but these substances, having been previously prepared,[5] were used in subsequent reactions without isolation and purification in order to avoid the losses incurred by these procedures. The pentaacetate of D-gulose was originally prepared by Frush and Isbell[6] from its calcium chloride salt. In the present work gulose pentaacetate was prepared from a hard, clear sirup of the sugar. The product did not readily crystallize and was used as a sirup.

The pentaacetates of the hexoses were converted to tetraacetylglycosyl halides.[7] Bromides[7a,c] were initially prepared from all of the pentaacetates, but when it was found that these derivatives of D-allose and D-altrose yielded only a trace of product in the subsequent coupling reaction with chloromercuri-6-benzamidopurine, the chlorides[7b,d] were prepared and were found to give improved yields. Because of their instability the halosugars were not isolated but were used as dry sirups immediately after they were obtained.

Condensation of the sirupy acetohalosugars with chloromercuri-6-benzamidopurine was brought about in refluxing xylene.[8] Because this condensation was carried out using ester derivatives of the carbohydrate, it was anticipated that the nucleosides derived from D-mannose, D-talose, and D-altrose would have an α-configuration, rather than the naturally occurring β-configuration, and the nucleosides obtained from D-gulose and D-allose would have a β-configuration. The directive effect of the ester group is described by the *trans* rule[9] which states that the incoming nucleophile couples at C-1 *trans* to the acyloxy group at C-2. Subsequent investigation of the configuration of the nucleosides, as described in the following, verified the prediction and further confirmed the reliability of the *trans* rule. In a recent paper,[10] the preparation of β-nucleosides from benzyl derivatives of α-chloro sugars is described, thus eliminating the directive influence of acyloxy groups. Preparation of similar, but as yet unknown, derivatives of D-talose and D-altrose may make it possible to synthesize β-nucleosides from these sugars.

(4) R. U. Lemieux and C. Brice, *Can. J. Chem.*, **34**, 1006 (1956).

(5) (a) N. K. Richtmyer and C. S. Hudson, *J. Am. Chem. Soc.*, **63**, 1727 (1941); (b) W. W. Pigman and H. S. Isbell, *J. Res. Natl. Bur. Std.*, **19**, 189 (1937).

(6) H. L. Frush and H. S. Isbell, *ibid.*, **35**, 111 (1945).

(7) (a) R. G. Hansen, W. J. Rutter, and P. Krichevsky in "Biochemical Preparations," Vol. 4, W. W. Westerfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p. 1; (b) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 967 (1948); (c) C. E. Redemann and C. Niemann in "Organic Synthesis," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p. 11; (d) B. R. Baker and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5900 (1955).

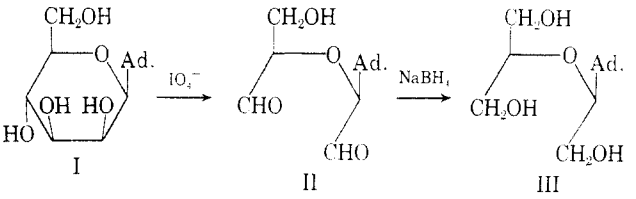
(8) J. Davoll and B. A. Lowy, *ibid.*, **73**, 1650 (1951).

(9) B. R. Baker in Ciba Foundation Symposium "Chemistry and Biology of Purines," G. E. W. Wolstenholme and C. M. O'Connor, Ed., Little, Brown and Co., Boston, Mass., 1957, p. 120.

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

Methanolic sodium methoxide was used to remove the blocking acyl groups from the crude products obtained after condensation of the halosugar with the adenine derivative. The nucleosides produced were extracted into water from which the final products from mannose, allose, and talose were obtained. In order to obtain the nucleosides of gulose and altrose, however, it was necessary to prepare the picrate salts and regenerate the nucleosides from them.[11]

Determination of the structure at the anomeric carbon atom of the carbohydrates was carried out by studies of the optical rotation following oxidation with periodate[2] and reduction with sodium borohydride.[12] 9-β-D-Mannopyranosyladenine (I),[13] the structure of which had been unequivocably established,[2] was used as a reference compound. When treated with periodate, α-(adenine-9)-α′-hydroxymethyldiglycollic dialdehyde (II) was formed.



This substance has two asymmetric carbon atoms and is expected to be formed from all D-aldohexopyranosyladenine nucleosides with a β-configuration. Nucleosides with an α-configuration would yield a diastereoisomer having a different rotation. Reduction of the dialdehyde yields a trialcohol, 2-*O*-[1-(9-adenyl)-2-(hydroxy)ethyl]glycerol (III), having only one asymmetric carbon atom at the position which was originally the anomeric carbon atom of the carbohydrate. Therefore, after periodate oxidation and reduction, anomeric nucleosides will yield compounds having optical rotations of equal value but of opposite sign.

Table I shows the results of the studies of the optical rotations of the nucleosides treated in this manner. Based on these results, as compared with the results obtained from the reference compound, the anomeric configuration of the nucleosides were assigned as shown. These results further verify the *trans*-directive effect of the C-2 acyloxy group.

TABLE I

POLARIMETRIC STUDIES OF PYRANOSYL NUCLEOSIDES

Nucleoside	[α]D after IO_4^- cleavage,[b] deg.	[α]D after $NaBH_4$ reduction,[c] deg.
9-β-D-Mannopyranosyladenine[a]	−19	+57
9-β-D-Allopyranosyladenine	−20	+58
9-β-D-Gulopyranosyladenine	−13	+57
9-α-D-Mannopyranosyladenine	−6	−58
9-α-D-Talopyranosyladenine	−1	−59
9-α-D-Altropyranosyladenine	−4	−57

[a] Reference compound, see footnotes 2 and 13. [b] Based on the dry weight of the dialdehyde product. [c] Based on the dry weight of the trialcohol product.

Biological Studies.—Preliminary screening studies of

(11) B. R. Baker and K. Hewson, *ibid.*, **22**, 959 (1957).

(12) R. S. Wright, G. M. Tener, and H. G. Khorana, *J. Am. Chem. Soc.*, **80**, 2004 (1958).

(13) The authors are indebted to Lord Todd for his generous gift of this substance.

these nucleosides were carried out by the standard plate assay procedure.[14] In the presence of up to 100γ of material, no activity was evidenced toward either a number of bacteria (*Bacillus subtilis, Mycobacterium avium, Staphylococcus aureus, Streptococcus fecalis, Klebsiella pneumoniae, Proteus vulgaris, Escherichia coli*, and *Pseudomonas aeruginosa*), a number of fungi (*Candida albicans, Kloeckera brevis, Trichophyton mentagrophytes, Penicillium oxalicum, Fusarium, Helminthosporium*, and *Nocardia asteroides*), protozoa, parasites, and algae (*Ochromonas malhamensis, Chlorella vulgaris, Tetrahymena pyriformis, Crithidia fasciculata*), or toward bacteriophage of *E. coli* and *S. aureus*.

Experimental[15]

Melting points were obtained on a Kofler micro hot stage and correspond to corrected values. Infrared spectra were measured on a Perkin-Elmer Infracord spectrophotometer and ultraviolet spectra on a Beckman Model DU. Optical rotations were determined in 100-mm. semimicro tubes using a Rudolph polarimeter, Model 70. Paper chromatograms of nucleosides were developed with 5% aqueous disodium hydrogen phosphate[16] (solvent 1) without the organic phase, and 1-butanol–water (86:14 v./v.)[17] (solvent 2) by a descending technique on Whatman No. 1 paper. Spots were located with a Mineralight lamp which produced ultraviolet radiation at 254 mμ.

D-Allose, D-altrose, D-gulose, and D-talose were prepared from the corresponding lactones by reduction with sodium amalgam in an acid medium as described by Frush and Isbell.[18] D-Allono-γ-lactone was prepared by the method of Pratt and Richtmyer[19] and the calcium altronate obtained from this procedure was used to prepare D-altrono-γ-lactone.[20] D-Talono-γ-lactone was prepared as described by Cretcher and Renfrew[21] and D-gulono-γ-lactone was purchased from Pfanstiehl Laboratories. The acetylation reagent[3] used was prepared by mixing acetic anhydride (137.1 ml.) and glacial acetic acid (58.5 ml.) at −17°. Concentrated sulfuric acid (4.56 ml.) was added as a catalyst.

α-D-Mannopyranose Pentaacetate.—From D-mannose (10 g., 55.6 mmoles) the pentaacetate was prepared by previously described methods.[3,22] There was obtained a yield of 15.2 g. (70%), m.p. 60–61°, $[\alpha]^{25}D$ +55.0° (*c* 4.0, $CHCl_3$) (lit.[22] m.p. 64°, $[\alpha]^{20}D$ +55.4°).

9-α-D-Mannopyranosyladenine.—α-D-Mannose pentaacetate (10 g., 25.6 mmoles) was converted to tetra-*O*-acetyl-D-mannopyranosyl bromide by modifications of earlier methods[7a,c] involving principally the use of acetic anhydride in place of glacial acetic acid. Evaporation of the solvent from the final ether extract yielded 4.7 g. of the sirupy glycosyl halide which was used to prepare 6-benzamido-9-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)purine by the method of Davoll and Lowy,[8] obtained as a yellow glass weighing 8.2 g. This material was dissolved in 120 ml. of hot absolute methanol, 7 ml. of 1 *N* methanolic sodium methoxide was added, and the mixture was refluxed for 1 hr. The reaction mixture was neutralized with glacial acetic acid, the solvents were removed by evaporation, and the residue obtained was partitioned between 100 ml. each of water and chloroform. The chloroform layer was further extracted 3 times with 50-ml. portions of water and the aqueous extracts were combined and concentrated under reduced pressure at 60°. During this process the product crystallized. The flask was chilled and the product removed by filtration and recrystallized from water to afford 2.09 g. (62% yield from the bromide) of beautiful plates, m.p. 146–148°. This material was recrystallized two more times from water to yield 1.61 g. of product, m.p. 147–149°, $[\alpha]^{26}D$ +73.5° (*c* 1.02, 1 *N* HCl). Paper chromatograms showed R_{ad} 1.58 in solvent 1 and 0.18 in solvent 2; ultraviolet and infrared spectra: $\lambda_{max}^{H_2O}$ 260 mμ (ε 14,600); λ_{max}^{KBr} (μ) 2.9 (NH, OH), 6.05, 6.2, 6.3, 6.7 (NH and purine ring), 9.0, 9.2, 9.35, and 9.54 (C–O–C, C–O–H).

Anal. Calcd. for $C_{11}H_{15}N_5O_5 \cdot H_2O$: C, 41.90; H, 5.43; N, 22.21; H_2O, 5.71. Found: C, 41.76; H, 5.43; N, 22.04; H_2O, 5.56.

D-Talopyranose Pentaacetate.—D-Talose (2.99 g., 16.6 mmoles) was converted to the pentaacetate.[3,22] Traces of acetic acid were removed by adding and distilling toluene three times, leaving a sirup which crystallized readily. The product, however, was used without isolation.

9-α-D-Talopyranosyladenine.—From the pentaacetate of talose the tetraacetyl bromide was prepared as described,[7a,c] yielding 7.1 g. of a hard sirup which was coupled with chloromercuri-6-benzamidopurine (8 g., 17 mmoles).[8] Following the procedure described for the preparation of mannopyranosyladenine, there was obtained, after recrystallization, 0.47 g. (10%) of white needles in two crops, m.p. 251–252°, $[\alpha]^{22}D$ +91.3° (*c* 3.00, 1 *N* HCl); R_{ad} 1.55 in solvent 1, 0.18 in solvent 2; ultraviolet and infrared spectra: $\lambda_{max}^{H_2O}$ 259 mμ (ε 15,200); λ_{max}^{KBr} (μ) 2.85, 2.95 (OH, NH), 6.05, 6.2, 6.3, 6.7 (NH and purine ring), 9.0–9.3, and 9.45–9.70 (C–O–C, C–O–H).

Anal. Calcd. for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.68; H, 5.20; N, 23.47.

D-Gulopyranose Pentaacetate.—To a hard, clear, colorless sirup of D-gulose (7 g., 38.8 mmoles) was added 150 ml. of ice-cold acetic anhydride and the sirup was triturated with a glass rod while 4.0 ml. of cold concentrated sulfuric acid was added dropwise. After 45 min. the sirup had dissolved. The flask was kept at room temperature for 3 days, poured onto ice chips, and the product was extracted 4 times with chloroform after stirring for 20 min. The chloroform extracts were combined, washed three times with saturated sodium bicarbonate solution, three times with water, and dried over sodium sulfate. Evaporation of the solvent left a sirup to which toluene was added and removed three times *in vacuo* to remove traces of acetic acid. A hard sirup was obtained which was used as the starting material for the next step.

9-β-D-Gulopyranosyladenine.—From the pentaacetate of gulose, tetraacetylgulopyranosyl bromide was prepared[7a,c] and condensed with chloromercuri-6-benzamidopurine.[8] An aqueous extract, obtained from a chloroform solution of the product after treatment with methanolic sodium methoxide to remove blocking groups, was concentrated to a sirup weighing 6.7 g. The sirup was dissolved in 40 ml. of absolute methanol and 90 ml. of 10% methanolic picric acid was added.[11] The flask was immersed in an ice bath for 3.5 hr., the product was removed by filtration, and washed with cold methanol and cold water. Recrystallization from water yielded 4.1 g. (26%) of the picrate. This compound softened at 206°, and melted slowly with decomposition up to 226°, $[\alpha]^{21}D$ −5° (*c* 4.24, dimethylformamide).

Anal. Calcd. for $C_{17}H_{18}N_8O_{12}$: C, 38.79; H, 3.45; N, 21.29. Found: C, 38.29; H, 4.22; N, 20.56.

From the picrate, 9-β-D-gulopyranosyladenine was prepared,[11] which, after recrystallizing twice from water, weighed 1.19 g. (17%), m.p. 212–213°, $[\alpha]^{22}D$ −15.2° (*c* 3.03, 1 *N* HCl); paper chromatography: R_{ad} 1.61 in solvent 1, and 0.28 in solvent 2; ultraviolet and infrared spectra: $\lambda_{max}^{H_2O}$ 259 mμ (ε 14,800); λ_{max}^{KBr} (μ) 2.9 (OH, NH), 6.05, 6.24, 6.36, 6.74 (NH and purine ring), 9.2–9.55 (C–O–C, C–O–H).

Anal. Calcd. for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.50; H, 5.16; N, 23.42.

β-D-Allopyranose Pentaacetate.—D-Allose (5.5 g., 30.6 mmoles) was acetylated as described.[3,22] The product was crystallized from ethyl ether after petroleum ether had been added and the solution cooled to give 5.4 g. (45%) of product, m.p. 93–93.5°, $[\alpha]^{21}D$ −13.7° (*c* 5.12, $CHCl_3$).

Anal. Calcd. for $C_{16}H_{22}O_{11}$: C, 49.23; H, 5.68. Found: C, 49.27; H, 5.74.

This material appears to be the same product obtained by Lemieux and Brice[4] by a base-catalyzed acetylation [lit.[4] m.p. 97–100°, $[\alpha]D$ −14.6° (*c* 1.5, $CHCl_3$)].

9-β-D-Allopyranosyladenine.—Tetraacetylallopyranosyl chloride was prepared from the pentaacetate[7b,d] and immediately

(14) (a) G. E. Foley, G. W. Kidder, V. C. Dewey, and P. S. Thayer, *Ann. N. Y. Acad. Sci.*, **76**, 413 (1958); (b) S. H. Hutner, H. A. Nathan, S. Aaronson, H. Baker, and S. Scher, *ibid.*, **76**, 457 (1958).

(15) Elementary analyses were determined at the Spang Microanalytical Laboratory, Ann Arbor, Mich., or at Midwest Microlab, Inc., Indianapolis, Ind.

(16) C. E. Carter, *J. Am. Chem. Soc.*, **72**, 1466 (1950).

(17) R. Markham and J. D. Smith, *Biochem. J.*, **45**, 294 (1949).

(18) H. L. Frush and H. S. Isbell, *J. Res. Natl. Bur. Std.*, **54**, 267 (1955).

(19) J. W. Pratt and N. K. Richtmyer, *J. Am. Chem. Soc.*, **77**, 1906 (1955).

(20) C. W. Austin and F. L. Humoller, *ibid.*, **56**, 1153 (1934).

(21) L. H. Cretcher and A. G. Renfrew, *ibid.*, **54**, 1590 (1932).

(22) C. S. Hudson and J. K. Dale, *ibid.*, **37**, 1280 (1915).

condensed with chloromercuri-6-benzamidopurine.[8] After removal of the blocking groups with methanolic sodium methoxide and neutralization with glacial acetic acid the product crystallized. Additional product was obtained by concentration of the mother liquor to a sirup which was triturated with water. The combined material was recrystallized three times from water to give 820 mg. (20% from β-D-allose pentaacetate) of product. This material decomposed between 273–315°, $[\alpha]^{24}D$ −8.0° (*c* 3.25, 1 *N* HCl). Paper chromatography with solvent 1 gave an R_{ad} 1.66 and 0.13 in solvent 2; ultraviolet and infrared spectra: $\lambda_{max}^{H_2O}$ 258 mμ (ε 14,700); λ_{max}^{KBr} (μ) 2.9 (OH, NH), 6.05, 6.25, 6.3, 6.7 (NH and purine ring), 9.0, 9.15, 9.35, 9.55 (C–O–C, C–O–H).

Anal. Calcd. for $C_{11}H_{15}N_5O_5 \cdot 0.5H_2O$: C, 43.13; H, 5.23; N, 22.87; H_2O, 2.94. Found: C, 43.14; H, 5.12; N, 22.70; H_2O, 2.86.

D-Altropyranose Pentaacetate.—D-Altrose (7.67 g., 42.6 mmoles) was acetylated as described.[3,22] A thick sirup (16.0 g.) was obtained which crystallized easily but the product was not isolated.

9-α-D-Altropyranosyladenine.—Tetraacetylaltropyranosyl chloride was prepared from the pentaacetate[7b,d] and condensed with chloromercuri-6-benzamidopurine.[8] Following removal of the blocking groups with methanolic sodium methoxide, the picrate was prepared.[11] After recrystallization from water 7 g. (42%) of the picrate was obtained as tiny needles which decomposed between 182–270°, $[\alpha]^{21}D$ +9° (*c* 3.40, dimethylformamide).

Anal. Calcd. for $C_{17}H_{18}N_8O_{12}$: C, 38.79; H, 3.45; N, 21.29. Found C, 37.94; H, 3.48; N, 23.21.

9-α-D-Altropyranosyladenine was regenerated from the picrate[11] and crystallization occurred on concentration of the aqueous solution. After recrystallizing twice from water 1.38 g. (15%) of product was obtained, m.p. 156–158°, $[\alpha]^{20}D$ +22.0° (*c* 3.50, 1 *N* HCl); R_{ad} 1.65 in solvent 1 and 0.14 in solvent 2; ultraviolet and infrared spectra: $\lambda_{max}^{H_2O}$ 259 mμ (ε 16,000); λ_{max}^{KBr} (μ) 2.9 (OH, NH), 6.1, 6.3, 6.7 (NH and purine ring), and 9.0–9.55 (C–O–C, C–O–H).

Anal. Calcd. for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.25; H, 5.12; N, 23.52.

Polarimetric Studies.—A solution of 16–20 mg. of each nucleoside in 1 ml. of hot water was prepared, cooled to room temperature, and 0.65 ml. of 0.25 *M* sodium metaperiodate was added. The volume was adjusted to 2 ml. and the solution was permitted to stand in the dark for 40–48 hr. until a constant optical rotation was reached. The solution was treated with 80 mg. of sodium borohydride and, after 0.5 hr., 1 ml. of 10% acetic acid solution was very carefully added. After the bubbling had ceased and the solution had reached room temperature, the specific rotation was again determined. The results of these determinations are shown in Table I in which 9-β-D-mannopyranosyladenine was used as the reference compound.

Polarimetric studies of the periodate oxidation product derived from 9-β-D-mannopyranosyladenine have been reported (lit.[8] $[\alpha]^{21}D$ −20.8°) as have the oxidation and reduction products of adenosine (lit.[12] $[\alpha]^{20}D$ +66°) and 9-α-D-ribofuranosyladenine (lit.[12] $[\alpha]^{20}D$ −66°).

Synthetic Schistosomicides. VI. 4-Substituted 1-(Dialkylaminoalkylamino)naphthalenes[1]

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Various 4-substituted 1-(dialkylaminoalkylamino)naphthalene compounds have been prepared as potential antischistosome agents. 4-[(2-Diethylaminoethyl)amino]-1-naphthol (XIV) was synthesized according to the following scheme. Treatment of 2,2,2-trifluoro-N-(4-hydroxy-1-naphthyl)acetamide (X) with dihydropyran gave 2,2,2-trifluoro-N-{4-[(tetrahydropyran-2-yl)oxy]-1-naphthyl}acetamide (XI), which upon alkaline hydrolysis afforded 4-[(tetrahydropyran-2-yl)oxy]-1-naphthylamine (XII). Alkylation of XII with 2-chlorotriethylamine gave N,N-diethyl-N′-{4-[(tetrahydropyran-2-yl)oxy]-1-naphthyl}ethylenediamine (XIII), which was converted into XIV with acid. Two N-(dialkylaminoalkyl)napthionic acids (XVa and b) were prepared from 1-naphthol-4-sulfonic acid and the appropriate dialkylaminoalkylamine. N,N-Diethyl-N′-(4-chloro, 4-methoxy-, 4-methylthio-, and 4-phenylthio-1-naphthyl)ethylenediamine (XVIa–d) were synthesized by alkylation of the appropriate 4-substituted 1-naphthylamine with 2-chlorotriethylamine. Various N,N-dialkyl-N′-(4-nitro-1-naphthyl)alkylenediamines (XVIIa–d) were obtained by the condensation of 1-chloro-4-nitronaphthalene with the requisite dialkylaminoalkylamine. Treatment of N,N-diethyl-N′-(4-nitro-1-naphthyl)ethylenediamine (XVIIa) with methyl iodide and benzyl chloride gave the corresponding quaternary salts XVIIIa and b.

1,4-Naphthoquinones inhibit the glycolysis of adult *Schistosoma mansoni in vitro* at low concentrations.[2,3] A similar mode of action has been postulated for the 1-amino-4-naphthylazo schistosomicides (Ia and b),[1,4–7] which can exist in quinoid form (IVa and b), and for various potential metabolites thereof (Chart I).[1]

The initial step of one likely metabolic pathway involves reduction to the corresponding 1,4-naphthalenediamines (IIa and b).[1] Indeed, certain N-(dialkylaminoalkyl)-1,4-naphthalenediamines (IIb) are more active against schistosomes and less toxic for mice than the N,N-dialkyl-N′-(4-phenylazo-1-naphthyl)alkylenediamines from which they are derived.[1] However, the 1,4-naphthalenediamines are very susceptible to oxidation and are unstable both in acidic and in basic media. Although the decomposition products of the naphthalenediamines have not yet been isolated and characterized, it is likely that oxidation products such as the N′-(1,4-dihydro-4-imino-1-naphthylidene)-N,N-dialkylalkylenediamines (IIIb) are formed initially. Subsequent hydrolysis would lead to N-[(dialkylamino)alkyl]-1,4-naphthoquinone imines (VIb) or 1,4-naphthoquinone imine (VIa), and ultimately to 1,4-naphthoquinone (IX). Similarly, oxidation of 1,4-naphthalenediamine (IIa)[2] would afford

(1) Previous paper: E. F. Elslager, D. B. Capps, L. M. Werbel, D. F. Worth, J. E. Meisenhelder, and P. E. Thompson, *J. Med. Chem.*, **7**, 487 (1964).

(2) E. Bueding, L. Peters, and J. F. Waite, *Proc. Soc. Exptl. Biol. Med.*, **64**, 111 (1947).

(3) E. Bueding and L. Peters, *J. Pharmacol. Exptl. Therap.*, **101**, 210 (1951).

(4) E. F. Elslager and D. F. Worth, *J. Med. Chem.*, **6**, 444 (1963).

(5) E. F. Elslager, D. B. Capps, L. M. Werbel, D. F. Worth, J. E. Meisenhelder, H. Najarian, and P. E. Thompson, *ibid.*, **6**, 217 (1963).

(6) E. F. Elslager, D. B. Capps, D. H. Kurtz, L. M. Werbel, and D. F. Worth, *ibid.*, **6**, 646 (1963).

(7) E. F. Elslager, D. B. Capps, D. H. Kurtz, F. W. Short, L. M. Werbel, and D. F. Worth, in preparation.