(c). A solution of X (1.1 g.) in methanol (20 ml.) was treated with 5 drops of concentrated hydrochloric acid and kept at room temperature for 2 hr. The solution was brought to dryness under reduced pressure and the residue, crystallized from boiling acetone, gave 6-(carbomethoxy)-purine (XI) 0.6 g. (69%), m.p. 226–227° dec.; R_f 0.57.

Anal. Calcd. for $C_7H_6N_4O_2$: C, 47.2; H, 3.3; N, 31.5. Found: C, 47.5; H, 3.6; N, 31.3.

Reaction of 6-Trichloromethylpurine with Ammonia.—A solution of ammonium bicarbonate (2 g.) in water (10 ml.) was treated dropwise with concentrated aqueous ammonia until its pH was about 9. To this was added II (1 g.) and the mixture was stirred at room temperature for 3 hr., with frequent additions of ammonia to maintain a pH of 9. The resulting solution was acidified with hydrochloric acid and the gummy precipitate was separated by decantation and dissolved in boiling water to which charcoal was added. Filtration and cooling gave 6-purinecarboxamide (XII) 0.2 g. (30%), m.p. 320–325° (reported 315–320° [5,25]); R_f 0.40.

Anal. Calcd. for $C_6H_5ON_5$: C, 44.2; H, 3.1; N, 42.9. Found: C, 44.4; H, 3.1; N, 43.0.

2-Methylthio-4-hydroxy-6-chloromethylpyrimidine.—A mixture of S-methylpseudothiourea sulfate (7 g.), ethyl γ-chloroacetoacetate (8.3 g.) and methanolic 2 *M* sodium methoxide (50 ml.) was stirred at room temperature for 12 hr. The solvents were removed under reduced pressure, and the residue was dissolved in water (100 ml.). Acidification with hydrochloric acid gave the above pyrimidine, 3.5 g. (40%), m.p. 180–181°, from methanol; λ_{max} 239, 290 mμ (in water).

Anal. Calcd. for $C_6H_7ON_2ClS$: C, 37.8; H, 3.7; N, 14.7; Cl, 18.7. Found: C, 37.8; H, 3.9; N, 14.8; Cl, 18.9.

West and Barrett[18] reported a m.p. of 230–235° for a product which they believed to be the above compound and which was unstable and, therefore, could not be obtained analytically pure. However, no evidence of instability in presence of water could be found for the compound described above.

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Acyclic Sugar Nucleoside Analogs. II. Sulfur Derivatives[1,2]

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The sulfur-containing, acyclic nucleoside analogs 1-(9-adenyl)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose (and D-glucose) aldehydrol (VIII, IX) have been prepared and characterized.

In a previous communication[2] we have described a pair of acyclic sugar nucleoside analogs which could be considered as derived from the aldehydrol (hydrate) of *aldehydo*-D-galactose pentaacetate. With few exceptions, penta-*O*-acetyl-*aldehydo*-D-galactose being one of them, the aldehydrol group is so unstable that it exists only in aqueous solution. Stable derivatives may, however, be obtained in which halogens, oxyacyl, oxyalkyl and thio-oxyalkyl groups are substituted for the hydroxyl groups. A number of these derivatives have been described.[3]

Penta-*O*-acetyl-1-bromo-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose aldehydrol (I) was first reported by Wolfrom and associates,[4] but is more easily prepared by the method of Gauthier[5] as adapted by Weygand and co-workers.[6] The corresponding D-glucose derivative (II) was prepared in this laboratory but failed to crystallize and was used in the synthesis described below as a sirup without further characterization.

We report herein the preparation of sulfur-containing acyclic nucleoside analogs by condensing the penta-*O*-acetyl-1-bromo-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose (D-glucose) aldehydrols (I, II) with 6-acetamido-9-chloromercuripurine (III)[7,8] by a procedure similar to that of Davoll and Lowy[7] for the synthesis of cyclic nucleosides. The products (IV, V) were purified through the crystalline picrates (VI, VII), the formation of which involves *N*-deacetylation.[9] The *O*-acetylated nucleoside analogs (X, XI) were regenerated from picrate salts (VI, VII) with an ion exchange resin. Deacetylation of X and XI with *n*-butylamine in boiling methanol solution produced 1-(9-adenyl)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose (and D-glucose) aldehydrols (VIII, IX). These substances were also obtained by deacetylation of the fully acetylated crude products (IV, V) with a boiling methanol solution of *n*-butylamine.

(1) Supported by Grant No. CY3232(C4) from the Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda 14, Maryland (R. F. Project 759D).

(2) Preceding paper in this series: M. L. Wolfrom, A. B. Foster, P. McWain, W. von Bebenburg, and A. Thompson, *J. Org. Chem.*, **26**, 3093 (1961).

(3) M. L. Wolfrom and D. I. Weisblat, *J. Am. Chem. Soc.*, **62**, 878 (1940).

(4) M. L. Wolfrom, D. I. Weisblat, and A. R. Hanze, *J. Am. Chem. Soc.*, **62**, 3246 (1940).

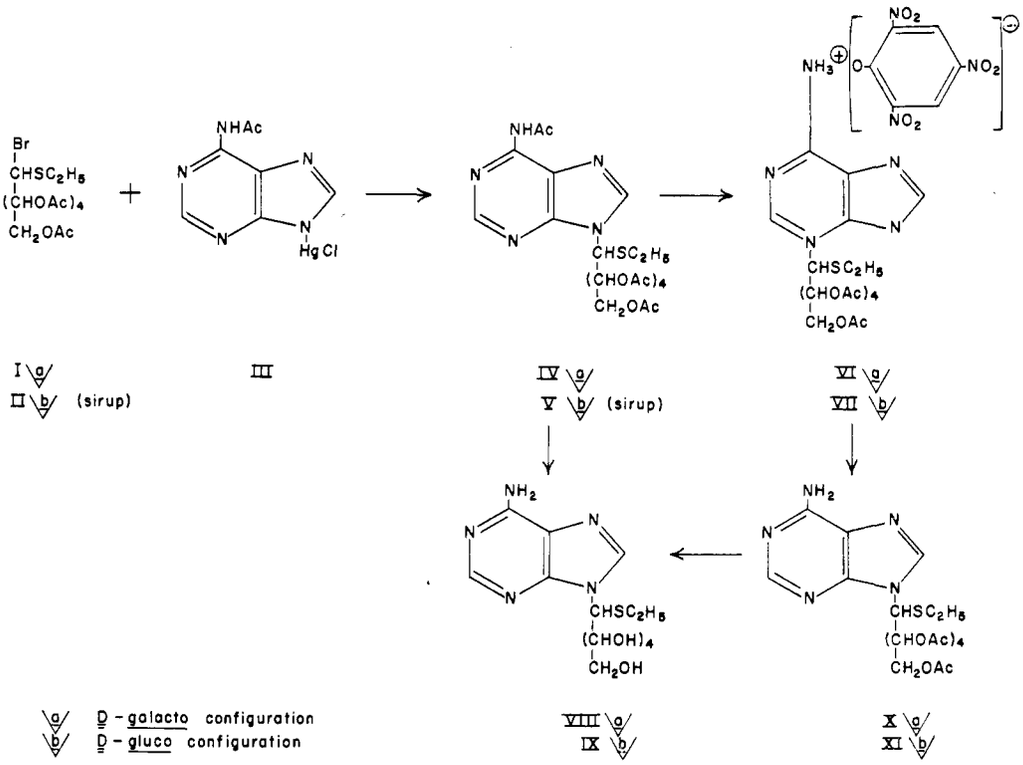
(5) B. Gauthier, *Ann. pharm. franc.*, **12**, 281 (1954); *Chem. Abstr.*, **48**, 13547 (1954).

(6) F. Weygand, H. Ziemann, and H. J. Bestmann, *Ber.*, **91**, 2534 (1958).

(7) J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.*, **73**, 1650 (1951).

(8) J. J. Fox, N. Yung, Iris Wempen, and Iris L. Doerr, *J. Am. Chem. Soc.*, **79**, 5060 (1957).

(9) J. R. Parikh, M. E. Wolff, and A. Burger, *J. Am. Chem. Soc.* **79**, 2778 (1957).



Experimental

1-(6-Acetamido-9-purinyl)penta-*O*-acetyl-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose Aldehydrol (IV).—Penta-*O*-acetyl-1-bromo-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose aldehydrol (I) was prepared by the method of Weygand and co-workers[6] and converted to a blocked acyclic sugar nucleoside by the general method of Davoll and Lowy.[7] A mixture of 24.0 g. of 6-acetamido-9-chloromercuripurine (III),[7] 20 g. of cadmium carbonate, 5 g. of Celite,[10] and 300 ml. of toluene was dried by the codistillation of 100 ml. of toluene. To this suspension, 31 g. of penta-*O*-acetyl-1-bromo-1,1-dideoxyethylthio-*aldehydo*-D-galactose aldehydrol (I) was added with stirring and the mixture was heated under reflux for 4.5 hr. The hot suspension was filtered and the filtrate was concentrated under reduced pressure to a sirup. Both the filter cake and residue from the filtrate were extracted with hot chloroform which was washed twice with 30% aqueous potassium iodide, and thrice with water. The dried chloroform solution was evaporated under reduced pressure to a sirup which crystallized; yield 34.7 g. (97.5% based on 6-acetamido-9-chloromercuripurine). The light brown solid was recrystallized from ether. Pure material was obtained by recrystallizing from toluene, after carbon treatment, to form light cream-colored platelets of IV; m.p. 151–152°, $[\alpha]^{23}D$ −62° (*c* 0.82, chloroform), λ_{max}^{EtOH} 274 mμ[11,12]; λ_{max}^{KBr} 3.18 μ (NH), 5.80 μ (ester carbonyl), 5.95 μ (amide), 6.24, 6.84 μ (purine ring), 7.32 μ (methyl hydrogen), 9.05, 9.25, 9.55, 9.70 μ (COC); x-ray powder diffraction data[13]: 8.47 vs (2), 6.86 m, 6.37 w, 5.45 vs (1), 4.72 w, 4.22 m (3), 3.76 w, 3.47 m, 3.22 w, 3.00 vw.

Anal. Calcd. for $C_{25}H_{33}N_5O_{11}S$: C, 49.10; H, 5.44; N, 11.44; S, 5.24. Found: C, 50.01; H, 5.44; N, 11.20; S, 5.45.

Penta-*O*-acetyl-1-(9-adenyl picrate)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose Aldehydrol (VI).—The crude, blocked nucleoside (IV) was *N*-deacetylated and converted to a crystalline picrate by the method of Parikh, Wolff, and Burger.[9] A sample of IV (10.4 g.) was dissolved in 60 ml. of warm ethanol and treated with 41 ml. (1 mole) of 10% ethanolic picric acid and the mixture was heated to boiling for 1 min. Upon cooling to 0°, a bright yellow, crystalline precipitate formed which was filtered and washed with cold ethanol; yield 6.34 g. (47%) of crude VI. Recrystallization from chloroform–ethanol solution by slow evaporation gave pure material; m.p. 196–197°.

Anal. Calcd. for $C_{29}H_{34}N_8O_{17}S$: N, 14.04; S, 4.01. Found: N, 14.70; S, 3.83.

Penta-*O*-acetyl-1-(9-adenyl)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose Aldehydrol (X).—The crystalline picrate (VI, 6.2 g.) was suspended in 350 ml. of warm 50% aqueous acetone and stirred with an excess (100 ml.) of moist Dowex-1 ($CO_3^=$)[14] anion exchange resin. The resulting faintly yellow solution was passed through a column (100 × 20 mm.) of Dowex-1 ($CO_3^=$) and concentrated under reduced pressure to 200 ml. The suspension was extracted twice with 100-ml. portions of chloroform. The extract was dried with anhydrous sodium sulfate and concentrated under reduced pressure to a crystalline solid (X); yield 2.91 g. (66%). Recrystallization (carbon) from ethanol produced colorless needles; m.p. 186–187°, $[\alpha]^{21}D$ −60° (*c* 0.51, chloroform); absorption spectral data[11,12]: λ_{max}^{EtOH} 262 mμ; λ_{Max}^{KBr} 2.95, 3.12 μ (NH, NH_2), 5.70 μ (ester carbonyl), 5.92, 6.07, 6.20, 6.32, 6.75 μ (NH_2, NH and purine ring), 7.27 μ (methyl hydrogen), 8.20 μ (COC of acetates), 9.27, 9.55 μ (COC); x-ray powder diffraction data[13]: 13.4 m, 9.30 m (3), 6.85 vs (1), 6.09 w, 5.59 vw, 4.99 s (2), 4.39 vw, 3.83 vw, 3.43 m, 3.29 w, 3.09 w, 2.79 vw.

(10) A product of the Johns-Manville Co., New York, N. Y.

(11) The ultraviolet spectral data were obtained on a Cary recording spectrophotometer, Model 10, Applied Physics Corp., Pasadena, California. The infrared spectral data were obtained with an infrared spectrophotometer, Model B, Baird Associates, Inc., Cambridge, Mass.

(12) W. B. Neely, *Advan. Carbohydrate Chem.*, **12**, 13 (1957); B. R. Baker and Kathleen Hewson, *J. Org. Chem.*, **22**, 959 (1957).

(13) Interplanar spacing, Å., CuKα radiation. Relative intensity, estimated visually: s, strong; m, medium; w, weak; v, very; three strongest lines numbered: 1, strongest.

(14) A product of the Dow Chemical Co., Midland, Michigan.

Anal. Calcd. for $C_{23}H_{31}N_5O_{10}S$: C, 48.49; H, 5.49; N, 12.29; S, 5.63. Found: C, 48.64; H, 5.37; N, 12.30; S, 5.74.

1-(9-Adenyl)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose Aldehydrol (VIII).—Crystalline penta-*O*-acetyl-1-(6-acetamido-9-purinyl)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose aldehydrol (IV, 5.0 g.) was dissolved in 75 ml. of hot, dry methanol to which 1.5 ml. of *n*-butylamine[15] was added and the solution refluxed for 6 hr. A crystalline solid (VIII) separated upon cooling the solution; yield 2.66 g. (91%). The material was redissolved in water, treated with carbon, and evaporated to a sirup. Addition of ethanol and storing at 0° induced crystallization; yield 2.59 g. (88%), m.p. 217–218°, $[\alpha]^{22}D$ −114° (*c* 0.53, water); absorption spectra data[11,12]: $\lambda_{max}^{H_2O}$ 262 mμ; λ_{max}^{KBr} 2.86, 3.00 μ (OH, NH); 6.02, 6.18, 6.30, 6.72 μ (NH_2, NH, and purine ring); 7.34 (methyl hydrogen); 9.00, 9.38, 9.74 μ (COC, COH); x-ray powder diffraction data[13]: 10.10 vs (1), 6.68 vw, 6.17 vw, 5.56 m, 5.11 s (2), 4.68 w, 4.23 s (3), 3.75 w, 3.59 vw, 3.37 w.

Anal. Calcd. for $C_{13}H_{21}N_5O_5S$: C, 43.44; H, 5.89; N, 19.49; S, 8.92. Found: C, 44.02; H, 5.88; N, 19.57; S, 8.96.

The product VIII was also obtained by deacetylation of penta-*O*-acetyl-1-(adenyl)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose aldehydrol (X) with boiling methanolic *n*-butylamine solution as described above.

Penta-*O*-acetyl-1-(9-adenyl)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-glucose Aldehydrol (XI).—Sirupy penta-*O*-acetyl-1-bromo-1,1-dideoxy-1-ethylthio-*aldehydo*-D-glucose aldehydrol (II) was prepared by Weygand's method[6] as described above for the D-galactose derivative, and added to an azeotropically dried mixture of 6-acetamido-9-chloromercuripurine, 11 g. of cadmium carbonate, 4 g. of Celite,[10] and 300 ml. of toluene. The mixture was refluxed for 2.5 hr. with stirring and filtered. The product was isolated as described above for the D-galactose derivative (IV); yield 17.7 g. of a sirupy penta-*O*-acetyl-1-(6-acetamido-9-purinyl)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-glucose aldehydrol (V). The substance was purified through the crystalline picrate (VII) as described above for the D-galactose derivative (VI); yield 14.5 g. (63%) of VII, dec. 155–165°.

The substance (XI) was regenerated from its picrate (VII, 12.8 g.) by the procedure described above for the corresponding D-galactose derivative (VI); yield 8.33 g. (91%) of crystalline XI. Recrystallization from toluene produced pure material; m.p. 134–135°, $[\alpha]^{21}D$ −109° (*c* 0.74, chloroform); absorption spectra data[11,12]: λ_{max}^{EtOH} 262 mμ, λ_{max}^{KBr} 2.95, 3.10 μ (NH_2, NH), 5.68 μ (ester carbonyl), 5.95, 6.08, 6.22, 6.32, 6.73 μ (NH_2, NH, and purine ring), 7.30 μ (methyl hydrogen), 8.30 μ (*COC* of acetate), 9.32, 9.70 μ (*COC*); x-ray powder diffraction data[13]: 11.05 vw, 8.59 w, 7.44 vs (1), 6.94 m, 6.42 vw, 5.52 m (3), 5.20 vw, 4.99 vw, 4.44 m (2), 4.18 w, 3.48 w, 3.10 vw, 2.98 w, 2.76 w, 1.97 w.

Anal. Calcd. for $C_{23}H_{31}N_5O_{10}S$: C, 48.49; H, 5.49; N, 12.29; S, 5.63. Found: C, 49.17; H, 5.32; N, 12.14; S, 5.38.

1-(9-Adenyl)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-glucose Aldehydrol (IX).—Crude crystalline XI (6.12 g.) was dissolved in 80 ml. of dry methanol and 4 ml. of *n*-butylamine and refluxed for 5.5 hr. The resulting solution was evaporated thrice from methanol and the residue washed with boiling chloroform to give a glassy material; yield 3.91 g. (91%). Crystallization was effected from methanol and recrystallization from ethanol produced pure material (IX): m.p. 149–150°, $[\alpha]^{16}D$ −123° (*c* 0.45, water); absorption spectra data[11,12]: $\lambda_{max}^{H_2O}$ 261 mμ, λ_{max}^{KBr} 2.86, 2.95, 3.05 μ (OH, NH), 5.98, 6.18, 6.32, 6.74 μ (NH_2, NH, and purine ring), 7.27 μ (methyl hydrogen), 9.00, 9.14, 9.57μ (COH); x-ray powder diffraction data[13]: 13.00 m, 10.40 vw, 7.73 vs (1), 6.63 vw, 5.92 m (3), 4.87 w, 4.35 vs (2), 3.94 vw, 3.71 vw, 3.51 vw, 3.34 vw.

Anal. Calcd. for $C_{13}H_{21}N_5O_5S$: C, 43.44; H, 5.89; N, 19.49; S, 8.92. Found: C, 43.17; H, 5.76; N, 18.25; S, 8.55.

(15) E. J. Reist and B. R. Baker, *J. Org. Chem.*, **23**, 1083 (1958).

Preparation of Salicylic Acids by the Hydroxylation of Benzoic Acids

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Basic cupric salts of benzoic and the toluic acids decompose at 200–220° to give the corresponding salicylic acids. The hydroxyl group enters the ring at a position adjacent to the carboxyl group.

The carbonation of phenols to give aromatic hydroxy acids by the Kolbe-Schmitt reaction is well known. An excellent review by Lindsey and Jeskey has appeared recently.[1] The position adjacent to the hydroxyl group on the aromatic ring is the preferred place of entry. However, a small amount of *para* substitution frequently occurs and conditions are known which favor entry of the carboxyl group at the *para* position.[2]

A method has now been discovered for the preparation of salicyclic acids by the hydroxylation of the corresponding benzoic acid derivative. This was accomplished by the thermal decomposition of the basic cupric salt of the acid.

Copper Salts of Benzoic Acids.—Cupric salts of aromatic carboxylic acids have been prepared by the combination of equivalent amounts of the sodium or potassium salts of the acid and a soluble inorganic cupric salt in water solution.[3] The insoluble product was purified by thorough washing with water. Only certain *ortho*-substituted products were soluble enough in common organic solvents to permit a recrystallization.

We have found that cupric benzoate prepared in this manner was a mixture of normal cupric

(1) A. S. Lindsey and H. Jeskey, *Chem. Rev.*, **57**, 583 (1957).

(2) O. Baine, G. F. Adamson, J. W. Barton, J. L. Fitch, D. R. Swayampati, and H. Jeskey, *J. Org. Chem.*, **19**, 510 (1954).

(3) M. Crawford and F. H. C. Stewart, *J. Chem. Soc.*, 288 (1953).