Notes

Preparation of 9-α-D-Idofuranosyladenine[1]

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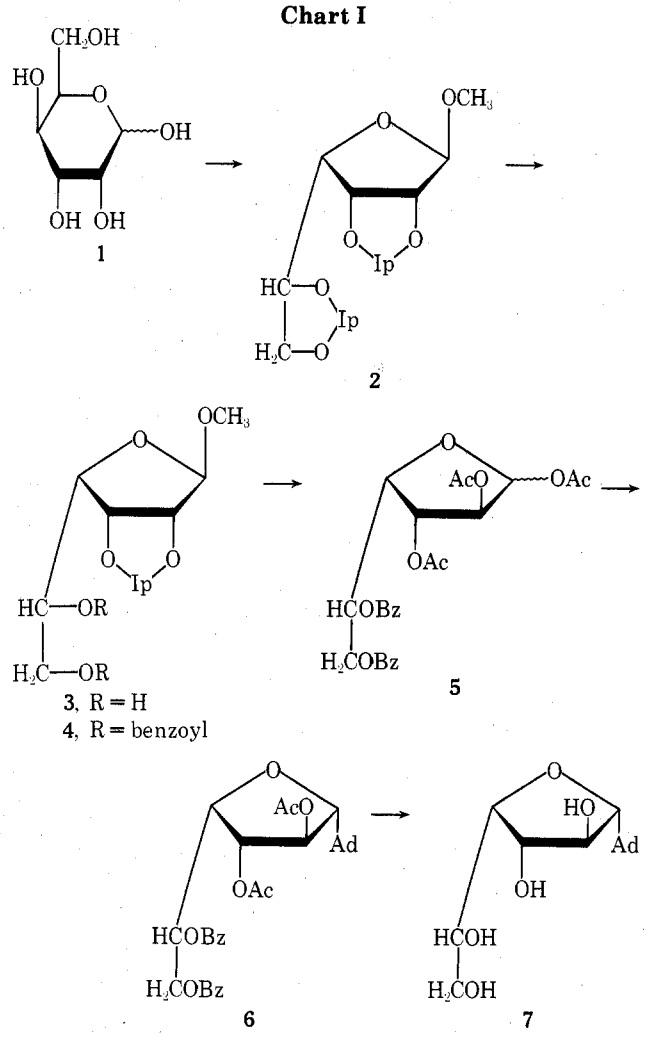
Hexofuranosyl nucleosides have been prepared as analogs[2] of the naturally occurring nucleosides with the intent of producing compounds of biological interest[3] as antitumor or antimicrobial agents. The only D-hexose which has not been transformed into a nucleoside of this type is D-idose, although the preparation of 9-α-L-idofuranosyladenine was reported a few years ago.[4] The problem with the preparation of the D nucleoside was that the route used[5] did not yield well-defined, characterizable intermediates that could be utilized for synthetic purposes. Although a simple method for preparing D-idose from D-glucose was developed some years ago,[6] the use of this source was considered impractical because the rather unstable free sugar would then have to be converted to the 1,2:5,6-di-*O*-isopropylidene derivative,[7] and this in turn transformed into a utilizable penta-*O*-acyl furanose derivative in a stepwise series of reactions similar to the route used by Baker and coworkers for the synthesis of 9-β-D-glucofuranosyladenine.[8]

A practical synthesis of a D-idofuranosyl nucleoside has now been accomplished by taking advantage of the commercial availability of D-gulono-1,4-lactone and the epimerization of C-2 of certain furanose derivatives when these are subjected to acetolysis conditions. In the present case, the conversion of a D-gulofuranose derivative to a penta-*O*-acyl-D-idofuranose derivative has been carried out and the latter converted to the title compound.

D-Gulose (**1**), which was prepared by reduction of D-gulono-1,4-lactone, was treated with a mixture of acetone, methanol, and 2,2-dimethoxypropane under acid conditions and subsequently subjected to partial hydrolysis to yield crystalline methyl 2,3-*O*-isopropylidene-β-D-gulofuranoside (**3**) in 59% yield[7] (Chart I). No particular advantage was accrued by isolation of the intermediate, methyl 2,3:5,6-di-*O*-isopropylidene-β-D-gulofuranoside (**2**), because no additional conditions of partial hydrolysis were found that would increase the yield of **3** any better than that reported here. The 5 and 6 hydroxyls were blocked by benzoylation, giving crude **4**. This was subjected to acetolysis under conditions which are known to cause epimerization of the C-2 position of glycofuranoses having three contiguous hydroxyl groups with the ring hydroxyls in a cis relationship.[10] The crude acetolysis product (**5**) was coupled with 6-benzamidochloromercuripurine by the titanium tetrachloride method[11] and the blocked nucleoside was isolated as a solid picrate of **6** after boiling with an ethanolic picric acid solution.[12] The picrate ion was removed with an anion exchange resin,[13] the blocking groups of **6** were removed with sodium methoxide in methanol, and the nucleoside, 9-α-D-idofuranosyladenine (**7**), was crystallized and found to have properties identical with those of the previously reported L enantiomer,[4] except for the sign of the optical rotation.

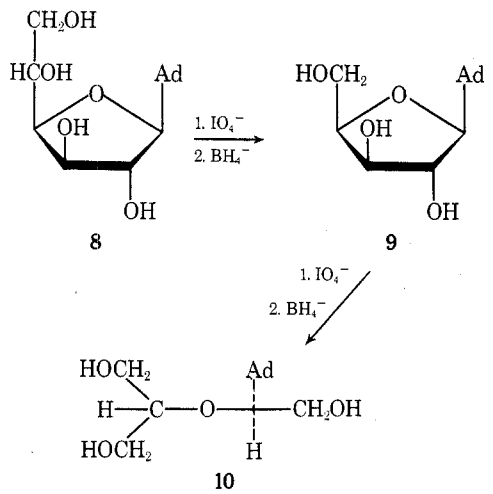
Previously, the anomeric configuration of 9-α-L-idofuranosyladenine (**8**)[4] had been assumed on the basis of the trans rule, in which the incoming base would form a bond trans to the hydroxyl group at C-2. Because of the greater availability of the L form **8** in this laboratory, it was used in the following experiment in order to determine the nature of the anomeric configuration. The reaction pathway utilized is shown in Chart II. It is generally recognized that vicinal hydroxyl groups in the trans configuration in furanose rings are very slowly oxidized in comparison to the exocyclic glycol group.[14] The former may require 4–7 days for completion, whereas the latter is completely oxidized in a matter of minutes. Therefore, **8** was subjected to periodate oxidation for a short time and then reduced with sodium borohydride to give a glassy substance, presumably 9-β-D-xylofuranosyladenine (**9**). Because the physical properties of this compound appeared to differ with each laboratory that prepared it,[15] the picrate was prepared which had a melting behavior similar to the literature value,[16] but whose optical rotation differed slightly. Therefore, compound **9** was regenerated from the picrate and the trialcohol **10** was prepared by extensive treatment of **9** with sodium periodate followed by reduction. The specific rotation of the final solution was +53° and was a good indication that the anomeric configuration of **9** was β-D, which meant

Chart I



Ad = adenine, Bz = benzoyl, Ip = $C(CH_3)_2$

Chart II



that the configuration of 8 was α-L. In the original work,[16] the anomeric configuration of **9** had not been proved directly, but was demonstrated using its precursor, 2,8-dichloro-9-β-D-xylofuranosyladenine. The latter was oxidized with periodate to a dialdehyde and its molecular rotation was compared to that of the dialdehyde derived from 2,8-dichloro-9-β-D-ribofuranosyladenine, treated the same way. Proof of the configuration of 8 meant that the configuration of the new nucleoside **7** must be assigned as α-D.

Experimental Section[17]

D-Gulose (1). D-Gulono-1,4-lactone (Pfanstiehl Laboratories, 30 g) was reduced to D-gulose (23 g) according to the general method of Wolfrom and Thompson.[18] The sugar was used as a clear, colorless syrup.

Methyl 2,3:5,6-Di-*O*-isopropylidene-β-D-gulofuranoside (2). D-Gulose (2.39 g) was dissolved in a refluxing mixture containing 13 ml of 2,2-dimethoxypropane, 8 ml of acetone, 8 ml of methanol, and 0.24 ml of concentrated hydrochloric acid. After 2 hr, the solution was cooled and poured slowly into 20 ml of saturated sodium bicarbonate solution. The organic solvents were evaporated and a white solid precipitated in the water. This was extracted with chloroform (3 × 25 ml) and dried, and the chloroform was evaporated. The syrup crystallized to afford 2.9 g (79%). Recrystallization from *n*-hexane gave the analytical sample as large, prismatic rods, mp 78.5–79°, $[\alpha]^{26}D$ −44.9° (*c* 1.39, chloroform). This compound was previously prepared by methylation of 2,3:5,6-di-*O*-isopropylidene-D-gulofuranose,[19] mp 75–76°, $[\alpha]D$ −44.9° (chloroform).

Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.09. Found: C, 56.88; H, 8.02.

Methyl 2,3-*O*-Isopropylidene-β-D-gulofuranoside (3). A mixture containing 20 g of D-gulose, 80 ml of 2,2-dimethoxypropane, 66 ml of methanol, 66 ml of acetone, and 2 ml of concentrated hydrochloric acid was heated at reflux for 2 hr. The solution was cooled to room temperature, 200 ml of water was added, and the organic solvents were removed by evaporation at 35°. A white precipitate formed in the aqueous layer which dissolved upon addition of 200 ml of methanol. Concentrated hydrochloric acid (5 ml) was added and after 1 hr the pH was adjusted to neutrality with saturated sodium bicarbonate solution (ca. 150 ml). The solution was evaporated to ca. 100 ml and extracted with chloroform (3 × 25 ml). The aqueous layer was then saturated with sodium chloride and extracted again with chloroform (3 × 25 ml). The extracts were combined and dried. Evaporation of the chloroform gave a white solid, 14.4 g (59%), of sufficient purity for further reactions. A small portion was recrystallized from ethyl acetate–*n*-hexane to give tiny needles, mp 77.5–79.5°, $[\alpha]^{20}D$ −83.5° (*c* 1.18, methanol). The compound had an ir spectrum identical with that of the L form, which was prepared from methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methanesulfonyl-α-D-mannofuranoside by the method of Evans and Parrish,[9] mp 76.5–77°, $[\alpha]D$ +82.3° (*c* 1.17, methanol) [obtained mp 78.5–80°, $[\alpha]^{22}D$ 2.5° (*c* 1.10, methanol)].

Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.74. Found: C, 51.18; H, 7.56.

9-α-D-Idofuranosyladenine (7). A solution of **3** (3.39 g) in 40 ml of dry pyridine was treated with 4.7 ml of benzoyl chloride and after 45 hr at room temperature the reaction mixture was poured into 300 ml of ice and saturated sodium bicarbonate solution. A gum formed which was extracted with chloroform (2 × 40 ml). The chloroform solution was washed with saturated sodium bicarbonate (100 ml) and water (100 ml), dried, and evaporated to a thin syrup. This was triturated with hot petroleum ether (bp 60–110°) and, after chilling, the solvent was decanted. This process was repeated one time and traces of solvent were evaporated to give **4** as a thick, orange syrup, 5.36 g (84%). The ir showed no hydroxyl peak, ir (film) 1718 (carbonyl), 1370 (*gem*-dimethyl), and 708 cm^{-1} (monosubstituted phenyl).

The entire sample was dissolved in a mixture containing 80 ml of acetic acid and 8 ml of acetic anhydride, and 4.4 ml of concentrated sulfuric acid was slowly added, dropwise, while the temperature of the solution was maintained below 20° with an ice bath. After 67 hr at room temperature, the dark solution was poured into 300 ml of ice and stirred until the ice melted. The milky mixture was extracted with chloroform (3 × 60 ml) and the chloroform solution was washed successively with saturated sodium chloride solution (2 × 150 ml), saturated sodium bicarbonate (200 ml), and again with saturated sodium chloride, and dried. All of the dark color was removed in the aqueous portions so that the chloroform solution was colorless. The chloroform was removed by evaporation and the syrup was coevaporated three times with benzene to afford a stiff gum of **5**, 3.6 g.

The gum was dissolved in 1,2-dichloroethane and coupled with 4.0 g of 6-benzamidochloromercuripurine in a reaction mixture containing 4 g of Celite 545, 1.2 ml of titanium tetrachloride, and 250 ml of 1,2-dichloroethane.[11] After work-up, as previously described,[4,11] a syrup was obtained which was dissolved in 30 ml of ethanol. To this solution was added 25 ml of 10% ethanolic picric acid, and the mixture was refluxed. After 5 min, an orange gum settled out of solution and additional ethanol was added to the boiling mixture until complete dissolution occurred again. Upon cooling to room temperature, a yellow solid slowly precipitated and the flask was stored in the refrigerator overnight. The product was obtained by filtration and immediately treated with Bio-Rad AG1-X8 (CO_3^{2-}) ion exchange resin in a solution of 80% aqueous acetone to remove the picrate ion. After filtration and treatment with Darco G-60, the solvents were evaporated to give a gum (1.49 g), which was dissolved in 50 ml of methanol, treated with 6 ml of 1 *N* methanolic sodium methoxide, and refluxed for 2 hr. The solution was neutralized with CG-120 (H^+) resin, filtered, and concentrated on a steam bath, during which crystallization occurred. After cooling, the product was filtered to yield 601 mg of **7** (14% yield from 3), mp 219–224°. Recrystallization from methanol raised the melting point to 226–226.5°, $[\alpha]^{26}D$ +38.1° (*c* 1.06, 1 *N* HCl). The L form **8** was reported[4] to have mp 228–228.5°, $[\alpha]^{26}D$ −39° (*c* 1.0, 1 *N* HCl). The ir spectra of **7** and **8** were identical.

Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.47; H, 5.11; N, 23.48.

Anomeric Configuration of 9-α-L-Idofuranosyladenine (8). A solution containing 100 mg of **8** in 2.5 ml of hot water was cooled to room temperature and 79 mg of sodium periodate in 2.5 ml of water was added. The mixture was kept in the dark for 1 hr and then poured into 60 ml of ethanol and stirred for 15 min, and the precipitate was removed by filtration. The solvents were evaporated, and the residue was dissolved in 5 ml of water and treated with 60 mg of sodium borohydride. The reaction proceeded for 1 hr, the solution was brought to pH 7 with Amberlite IR-120 (H^+) resin and filtered, and the water was evaporated, leaving a glass, 91 mg, $[\alpha]^{23}D$ −53°, presumably **9**.

The glass was dissolved in water and converted to a picrate with a saturated solution of picric acid in water, and recrystallized from boiling water, mp 210–220° with slow decomposition and sublimation, the sublimate forming star-like clusters on the cover slip which melted and further sublimed over 260°, $[\alpha]^{22}D$ −54.1° (*c* 0.74, pyridine).

Anal. Calcd for $C_{16}H_{16}N_8O_{11}$: C, 38.71; H, 3.25; N, 22.58. Found: C, 38.84; H, 3.35; N, 22.38.

The picrate ion was removed in hot water with Bio-Rad AG1-X8 (CO_3^{2-}) resin. Evaporation of the water gave 30.6 mg of a glass which was dissolved in 2.5 ml of 0.098 *M* aqueous sodium periodate solution and stored in the dark for 5 days. The solution was treated with 180 mg of sodium borohydride for 1 hr and neutralized with 20% aqueous acetic acid. The volume was adjusted to 5 ml, $[\alpha]^{23}D$ +53°. Considering inaccuracies involved in weighing the glass and the lengthy exposure to the oxidizing agent, this value is quite reasonable. When adenosine was treated in a similar manner,

a value of +66° was obtained,[20] but the pure trialcohol **10** had a value of +59°.[21]

Registry No.—**1**, 4205-23-6; **2**, 55520-69-9; **3**, 55520-70-2; **4**, 55520-71-3; **5**, 55520-72-4; **7**, 55555-40-3; **8**, 32653-60-4; **9**, 524-69-6; 9 picrate, 55520-73-5; 2,2-dimethoxypropane, 77-76-9; 2,3-*O*-isopropylidene-5,6-di-*O*-methanesulfonyl-α-D-mannofuranoside, methyl, 50692-25-6.

References and Notes

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(15) See Experimental Section of M. J. Robins, Y. Fouron, and R. Mengel, *J. Org. Chem.*, **39**, 1564)1974), for an extensive list of melting points and optical rotations. In addition, A. Magnani and Y. Mikuriya, *Carbohydr. Res.*, **28**, 158 (1973), report data on a methanol solvate of **9**.
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A Simple $RuCl_2(PPh_3)_3$-Catalyzed Synthesis of the 3,5,6,7-Tetrahydro-4(2*H*)-benzofuranone System

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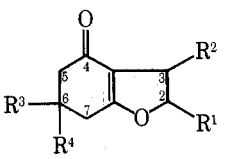
In a previous communication[1] we reported the selective transfer hydrogenation of one carbonyl group in cyclohexane-1,3-diones using ethylene glycol as hydrogen donor and $RuCl_2(PPh_3)_3$ as catalyst. The reduction is effective under conditions in which the dehydrogenated carbinol, the glycol aldehyde, is continuously removed from the reaction mixture during the process. (See footnote 5, ref 1). When the aldehyde is allowed to accumulate these cyclic diketones undergo a remarkable catalytic reaction whereby the title system is formed.

With the exception of the Claisen rearrangement of 3-allyloxy-2-cyclohexen-1-ones[2] that yields 2-methylated 3,5,6,7-tetrahydro-4(2*H*)-benzofuranones (isolated as semicarbazone derivatives), the known syntheses of **1**, and of its simple alkyl derivatives, are low yielding and give, in general, impure products.[3-7]

Our new one-pot synthesis of **1** is accomplished simply by refluxing cyclohexane-1,3-dione with excess ethylene glycol in the presence of some $RuCl_2(PPh_3)_3$. The method is not only extremely facile, but permits the isolation of the analytically pure bicyclic compound in a reasonable yield (64%). Similarly alkylated cyclohexane-1,3-diones can be converted to the corresponding substituted 3,5,6,7-tetrahydro-4(2*H*)-benzofuranones. 5,5-Dimethylcyclohexane-1,3-dione (dimedone) and 5-*tert*-butylcyclohexane-1,3-dione[8] give **2** and **3** in 40 and 27% yields, respectively.



1, $R^1 = R^2 = R^3 = R^4 = H$
2, $R^1 = R^2 = H; R^3 = R^4 = CH_3$
3, $R^1 = R^2 = R^3 = H; R^4 = C(CH_3)_3$
4, $R^2 = H; R^1 = R^3 = R^4 = CH_3$
5, $R^1 = H; R^2 = R^3 = R^4 = CH_3$

The reaction of dimedone with propane-1,2-diol afforded a mixture of 2,6,6- and 3,6,6-trimethyl-3,5,6,7-tetrahydro-4(2*H*)-benzofuranone (**4** and **5**, respectively) in a ratio of 3:1. Compounds **4** and **5**, however, proved difficult to separate.[9]

The catalysis is assumed to proceed by the following mechanism.