Note

Synthesis of 9-α- and 9-β-D-fucopyranosyladenine

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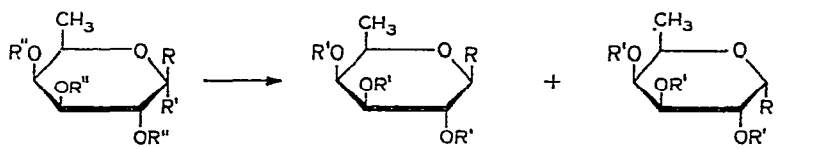
(Received February 24th, 1971; accepted April 23rd, 1971)

9-β-D-Fucopyranosyladenine (**5**) was required in this laboratory as a starting material in the synthesis of a potential inhibitor of adenosine deaminase. A recent note[1] on the synthesis of 9-β-L-fucopyranosyladenine has prompted this report of the synthesis of the enantiomer (**5**).

Tetra-*O*-acetyl-α-D-fucopyranose (**1**) was obtained in 65% yield by acetylation with the isomerization reagent described by Montgomery and Hudson[2]. The β-D anomer **2** was a syrup. Both **1** and **2** were coupled with 6-benzamidochloromercuripurine with the titanium tetrachloride method[3]. An intermediate, blocked nucleoside picrate **3** was characterized, and removal of the picrate ion afforded crystalline 9-(2,3,4-tri-*O*-acetyl-β-D-fucopyranosyl)adenine (**4**). Removal of the acetyl groups with methanolic sodium methoxide gave crystalline **5** containing 0.5 mole of methanol as solvate.



1 R=H; R'=R"=Ac
2 R=R"=Ac; R'=H

3 R=adeninyl.H$^+$ picrate; R'=Ac
4 R=adeninyl; R'=Ac
5 R=adeninyl; R'=H

6 R=adeninyl; R'=H

The α anomer **6** was isolated by workup of the mother liquors resulting from the crystallization of **3** and **4**. After deblocking, the nucleoside components were separated by the chromatographic procedure of Dekker[4] to give **6** and some additional **5**. The order of elution of **5** and **6** from the column was notable because the β-D anomer (**5**) was eluted well before the α-D anomer (**6**). This is the second time that this order of elution has been reported[5]; usually a β nucleoside will emerge from this column immediately after the α anomer, an observation which has been suggested as a proof of anomeric configuration[6].

Crystallization of **5** under the conditions described for the L form[1] were found to be unsuitable. Crystallization was finally achieved from a highly concentrated

solution of the nucleoside in methanol. It was expected from application of the *trans* rule[7] that **5** would have the β-D configuration. No further proof is offered here since the enantiomer of **5** has previously been shown by n.m.r. spectroscopy to have the β-L configuration[1].

EXPERIMENTAL

Melting points were determined on a Kofler micro hot-stage outfitted with a polarizing light microscope and correspond to "corrected melting point". Elementary analyses were determined by the Spang Microanalytical Laboratory, Ann Arbor, Michigan. Evaporations were performed *in vacuo* in a rotary evaporator at a bath temperature of 40–45°. T.l.c. was performed on Silica Gel HF plates (E. Merck A. G., Darmstadt) of 0.25-mm thickness, and the spots were located with a u.v. lamp.

1,2,3,4-Tetra-O-acetyl-α-D-fucopyranose (**1**). — D-Fucose (5 g) was acetylated in 60.1 ml of the acetylation reagent by methods described earlier[2,8]. The resulting syrup began to crystallize after being kept for several days. Recrystallization from ether gave 6.55 g (65%) in two crops, m.p. 94°, $[\alpha]_D^{25}$ +122° (*c* 1.04, chloroform); lit.[9]: m.p. 92–93°, $[\alpha]_D$ +129° (*c* 1.5, chloroform). For the L form, the following data have been reported: m.p. 93°, $[\alpha]_D^{20}$ −116° (*c* 1, chloroform)[10]; m.p. 92–93°, $[\alpha]_D^{34}$ −120° (*c* 2, chloroform)[11].

Anal. Calc. for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: C, 50.48; H, 5.97.

1,2,3,4-Tetra-O-acetyl-β-D-fucopyranose (**2**). — The mother liquor from the crystallization of **1** was evaporated to give a hard gum (2.11 g), $[\alpha]_D^{24}$ +47° (*c* 2.1, chloroform); lit.[10]: $[\alpha]_D$ −39° to −56° (chloroform) for the L form.

9-(2,3,4-Tri-O-acetyl-β-D-fucopyranosyl)adenine picrate (**3**). — The coupling reaction and workup were performed according to previously described methods[3]. The reaction mixture consisted of **1** (5.87 g, 17.6 mmoles), 6-benzamidochloromercuripurine (10.5 g, 22.2 mmoles), Celite-545 (10.5 g), titanium tetrachloride (2.5 ml), and 1,2-dichloroethane (750 ml). A light-yellow syrup (8.1 g) was obtained. This was dissolved in hot abs. ethanol (50 ml), and 10% ethanolic picric acid (41 ml) was added. The mixture was heated at reflux[12] for 20 min and allowed to cool slowly. After two days in the refrigerator, 5.02 g (44.4%) of picrate was obtained in two crops. The analytical sample was prepared by recrystallization of a small portion from ethanol–ethyl acetate, m.p. 222–224° (dec.); $[\alpha]_D^{24}$ −6.1° (*c* 1.05, acetone).

Anal. Calc. for $C_{23}H_{24}N_8O_{14}$: C, 43.40; H, 3.80; N, 17.61. Found: C, 43.13; H, 3.86; N, 17.83.

9-(2,3,4-Tri-O-acetyl-β-D-fucopyranosyl)adenine (**4**). — The picrate **3** (4.21 g) was dissolved in 80% aqueous acetone (500 ml) and the picrate ion was removed[13] with Bio-Rad (AG1-X8, CO_3^{2-}) resin. Evaporation to dryness (with the aid of abs. ethanol) yielded a crystalline mass which was recrystallized from ethyl acetate (2.32 g 71%), m.p. 234–236°. One more recrystallization raised the m.p. to 238–239°, with shrinking above 225° and formation of small droplets at 232°; $[\alpha]_D^{24}$ −5.5° (*c* 2.05, acetone); t.l.c.: R_F 0.55 (in 3:1 acetone–methanol), 0.09 (in ethyl acetate); λ_{max}^{MeOH} 258.5 nm. The product contained 1 mole of ethyl acetate bound as solvate.

Anal. Calc. for $C_{17}H_{21}N_5O_7 \cdot C_4H_8O_2$: C, 50.90; H, 5.90; N, 14.14. Found: C, 51.04; H, 5.94; N, 14.17.

Compound **4** was also prepared from **2** by the same procedure as that described for **1**. The reaction mixture consisted of **2** (2.1 g), 6-benzamidochloromercuripurine (3.8 g), Celite-545 (3.8 g), titanium tetrachloride (0.9 ml), and 1,2-dichloroethane (300 ml). The yellow syrup (3.25 g) obtained was converted into **3** (2.42 g, 61%), which in turn was converted into **4** (1.01 g, 84%), m.p. 238–240°.

9-β-D-Fucopyranosyladenine (**5**). — Compound **4** (1.46 g) was treated with 0.1M methanolic sodium methoxide at reflux for 1 h. The methanol was evaporated, the residue dissolved in water (40 ml), the solution neutralized with Dowex-50 (H^+), and the water evaporated. The residue was crystallized slowly from methanol (3–4 ml) to afford 634 mg of product as clusters of long rods. Concentration of the mother liquor gave an additional 59 mg (total yield: 88%). The m.p. behavior was somewhat unusual in that the clear, colorless crystals became frosted during heating and were opaque to polarized light at about 106–110°, whereupon a slight effervescence occurred. A slow change to an amorphous material ensued until a viscous liquid was slowly formed near 170°; $[\alpha]_D^{26}$ +10.9° (*c* 1.88, water); $\lambda_{max}^{pH\,1}$ 256.5 nm (ε 15,000), $\lambda_{max}^{H_2O}$ 259 nm (ε 14,800), $\lambda_{max}^{pH\,13}$ 259 nm (ε 15,000); t.l.c. in 3:1 chloroform–methanol, R_F 0.16.

Anal. Calc. for $C_{11}H_{15}N_5O_4 \cdot 0.5\ CH_3OH$: C, 46.45; H, 5.77; N, 23.56. Found: C, 45.91; H, 5.65; N, 23.71.

Fisher *et al.*[1] reported m.p. 271–275° for the nonsolvated L-enantiomer; $[\alpha]_D^{19}$ −11.8° (*c* 0.99, water); t.l.c. in 3:1 chloroform–methanol: R_F 0.19. When corrected for 5.4% of methanol, **5** had $[\alpha]_D^{26}$ +11.5°, which is in good agreement with that of the L form.

9-α-D-Fucopyranosyladenine (**6**). — The mother liquors from the crystallization of **3** (except for the original mother liquor, which was discarded) were pooled, and the picrate ion was removed as described for **4**. The syrup obtained was pooled with the mother liquors from the preparation of **4**. Crystallization from ethyl acetate gave an additional 196 mg of **4**. The yellow foam (1.06 g) obtained after evaporation of the solvent was treated with 0.1M methanolic sodium methoxide (30 ml) at reflux for 45 min. Neutralization with Dowex-50 (H^+) and evaporation of the solvent gave a residue, which was dissolved in water (40 ml) and washed with chloroform. The dark orange, aqueous layer was treated hot with Norit A, which removed most of the color. The water was evaporated and the residue dried by addition and evaporation of ethanol (530 mg). This was dissolved in a minimum amount of water and placed on a column (40 × 1 cm) of Bio-Rad AG1-X2 (200–400 mesh, OH^-) resin[4], which had been packed in water. Elution was performed with 40% aqueous methanol and 7-ml fractions were collected. Fractions 5–11 yielded 85 mg of compound **5** in two crops. Fractions 106–130 were combined and evaporated to dryness, whereupon crystallization occurred. The crystals were triturated with cold methanol, and filtered off. Recrystallization gave 48.3 mg in two crops as clusters of tiny platelets, m.p. 242.5–

243°; $[\alpha]_D^{26}$ −70.3° (*c* 0.95, water); $\lambda_{max}^{pH\ 1}$ 257 nm (ε 14,400), $\lambda_{max}^{H_2O}$ 259 nm (ε 14,700), $\lambda_{max}^{pH\ 13}$ 259 nm (ε 14,600); t.l.c. in 3:1 chloroform–methanol: R_F 0.31.

Anal. Calc. for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.98; H, 5.36; N, 24.67.

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