5′-Deoxy-2-fluoroadenosine (1)

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2-Fluoroadenosine (2) and other 9-D-furanosyl-2-fluoroadenines (3) have shown interesting biologic properties. 2-Fluoroadenosine is known to be converted *in vivo* to its mono-, di-, and triphosphate by adenosine kinase and nucleotide kinases (4,5), and, since mutant cells that lack adenosine kinase and cannot carry out this conversion are resistant to 2-fluoroadenosine (6), it would appear that the phosphates are the cytotoxic form of this agent. Thus it became of interest to prepare 5′-deoxy-2-fluoroadenosine (**9**) and study its biologic properties (7).

5-deoxy-D-ribose prepared by the method of Kissman and Baker (9), was converted to 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranose (**2**) by treatment with acetic anhydride in pyridine. Fusion of **2** with 2,6-dichloropurine in the presence of *p*-toluenesulfonic acid (3) gave 9-(2,3-di-*O*-acetyl-5-deoxy-D-ribofuranosyl)-2,6-dichloropurine as an anomeric mixture (2.6β:1α), which was resolved by column chromatography on silica gel. The β-anomer (**3**) was converted to the 2,6-diazidopurine nucleoside **4** by reaction with sodium azide in ethanol. Reduction of **4** with Pd/C followed by diazotization of the resultant diamino compound **5** in 48% fluoboric gave a mixture of 9-(2,3-di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-2-fluoroadenine (**6**) and 9-(2,3-di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-2,6-difluoropurine (**7**), along with some 5′-deoxycrotonoside diacetate (**8**). This mixture was purified by preparative tlc before treatment with alcoholic ammonia to give the desired 5′-deoxy-2-fluoroadenosine (**9**).

EXPERIMENTAL (10)

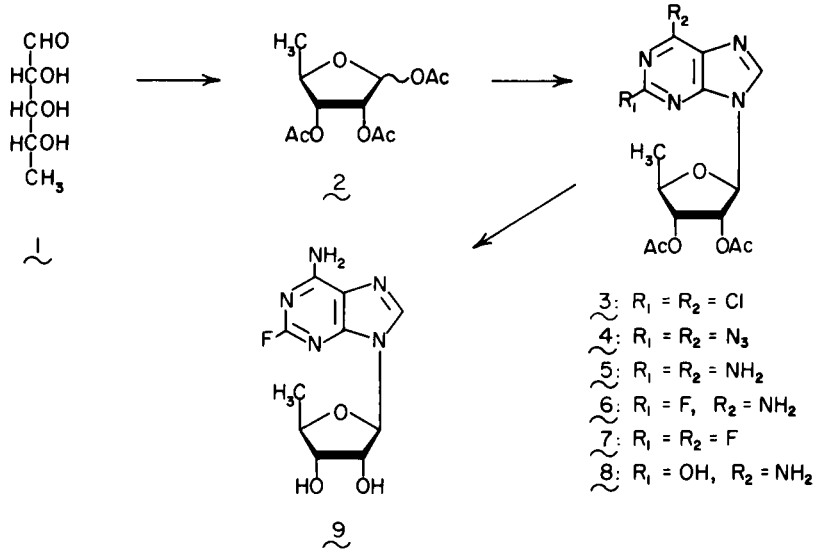
1,2,3-Tri-*O*-acetyl-5-deoxy-D-ribofuranose (**2**).

A mixture of 5-deoxy-D-ribose (9) (26.2 g., 0.19 mole) and acetic anhydride (136 ml.) in pyridine (910 ml.) was stirred for 3 days before it was poured slowly into cold saturated aqueous sodium bicarbonate (1800 ml.). The resulting solution was extracted with chloroform (4 l.), and the combined extracts were dried over magnesium sulfate. The chloroform was removed by rotary evaporation *in vacuo* and traces of pyridine by repeated evaporation with toluene. The residual syrup was distilled *in vacuo*; yield 14.0 g. (30%), b.p. 82-96°/0.05 mm.

Anal. Calcd. for $C_{11}H_{16}O_7$: C, 50.77; H, 6.20. Found: C, 50.74; H, 6.33.

9-(2,3-Di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-2,6-dichloropurine (**3**) and its α-Anomer.

To a melt of 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranose (7 g., 27 mmoles) and 2,6-dichloropurine (4.5 g., 24 mmoles) was added 100 mg. of *p*-toluenesulfonic acid, and the mixture was heated at 130° for ½ hour before it was cooled to room temperature and dissolved in benzene (100 ml.). The benzene solution was extracted with saturated aqueous sodium bicarbonate (50 ml.) and



then with water (150 ml., 55 ml.) before it was dried over magnesium sulfate. The concentrated benzene solution was applied to a silica gel column (2.8 x 85 cm.), which was eluted with benzene-ethyl acetate (3:1). From this column was obtained 8.06 g. (75%) of a mixture the α- and β-anomers that was partially resolved by this treatment. A second column run in the same manner completed the resolution giving a total of 5.82 g. (54%) of the β-anomer (**3**) and 2.22 g. (21%) of the α-anomer, both as glasses. The identity of these anomers was established by their pmr spectra; the signal from the anomeric proton of the α-anomer occurs at 6.65, downfield from that of the β-anomer, which occurs at 6.15 (11). The chromatographically homogenous β-anomer (**3**) was used in the next step without further purification.

9-(2,3-Di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-2,6-diazidopurine (**4**).

A solution of 9-(2,3-di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-2,6-dichloropurine (2.26 g., 5.8 mmoles) and sodium azide (755 mg., 11.6 mmoles) in 50 ml. of ethanol was refluxed for 1¼ hour. The insoluble salt was removed by filtration, and the solution was evaporated to dryness. The residue was triturated several times with benzene, and the benzene solution was evaporated to dryness giving a chromatographically homogenous glass (2.2 g., 94%), which was used in the next step without further purification.

9-(2,3-Di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-2,6-diaminopurine (**5**).

9-(2,3-Di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-2,6-diazidopurine (2.2 g., 5.6 mmoles) in alcohol (200 ml.) was reduced at room temperature and atmospheric pressure using 5% Pd/C catalyst. The reduction required 18 hours and three changes of the hydrogen atmosphere. After removal of the catalyst, the solution was concentrated whereupon a solid precipitated; yield, 1.4 g. (74%), m.p. 240°. This chromatographically homogenous material was diazotized without further purification.

9-(2,3,5-Tri-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-2-fluoroadenine (**6**) and 9-(2,3,5-tri-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-2,6-difluoropurine (**7**).

To a solution of 9-(2,3,5-tri-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-2,6-diaminopurine (1.96 g., 5.5 mmoles) in 48% fluoboric acid at -15° was added dropwise sodium nitrite (1.2 g., 16 mmoles) in 1.6 ml. of water, and the solution was stirred for an additional 40 minutes before the addition of 100 ml. of chloroform and neutralization at -20° with saturated sodium hydroxide. After neutralization was complete the chloroform layer was separated, washed with water, and dried over magnesium sulfate. The aqueous layer was extracted ethyl acetate and this extract washed with water and dried. The extracts were taken to dryness and the residual oils chromatographed on preparative tlc plates using benzene-ethyl acetate (1:1) as eluant. The nucleosides, obtained as oils and identified by uv and pmr spectroscopy as **6** (365 mg., 19%) and **7** (590 mg., 30%), were combined and deacetylated without further purification. In another experiment **6** was obtained as a crystalline solid, m.p. 208°.

5′-Deoxy-2-fluoroadenosine (**8**).

A mixture of 9-(2,3-di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-2-fluoroadenine (**6**) and 9-(2,3-di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-2,6-difluoropurine (**7**) (662 mg., 1.8 mmoles) suspended in 100 ml. of sieve-dried ethanol at 5° was treated with dry ammonia gas. The suspended solids dissolved and the solution was allowed to stand overnight at 5°. Rotary evaporation *in vacuo* to 20 ml. caused crystallization to occur. The crystals were collected by filtration, washed with ethanol, and dried; yield 313 mg. (65%), m.p. 256°. The crude material was recrystallized once with ethanol and once from water to give the analytical sample, yield 198 mg. (41%), m.p. 258°; $[\alpha]_D^{20}$ -50.0 ± 4.7° (*c* 0.15, ethanol); λ max in nm ($\epsilon \times 10^{-3}$) = 0.1 *N* hydrochloric acid 264 (14.0), 268 (sh); *p*H 7, 0.1 *N* sodium hydroxide 262 (15.2), 268 (sh).

Anal. Calcd. for $C_{10}H_{12}FN_5O_3$: C, 44.62; H, 4.50; N, 26.02. Found: C, 44.33; H, 4.67; N, 25.74.

REFERENCES

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(7) Evidence has been presented for the cellular cleavage of 2-fluoroadenosine to 2-fluoroadenine which can be converted to its ribonucleotide by adenine phosphoribosyltransferase (6,7). This ambiguity is no problem, since mutant cells lacking adenine phosphoribosyltransferase are available (8).

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(10) SilicAR-TLC-7 (Mallinckrodt) was used for column and thin layer chromatographic purifications. Silica gel H (Brinkmann) was used for thin layer analyses. Spots were detected with either uv light after spraying the plates with ultraphor WT (BASF Color & Chemicals, Inc., Charlotte, N. C.) or heat charring after spraying the plates with ammonium sulfate. The uv spectra were determined in the solvents specified with a Cary Model 14 spectrophotometer and the pmr spectra were determined in deuteriochloroform with a Varian A-60A spectrometer (TMS) (these spectra, which are in agreement with the assigned structures, are not presented). Melting points were determined on a Kofler-Heizbank and are corrected.

(11) For a discussion of the assignment of the anomeric configuration of 9-D-furanosylpurines see J. A. Montgomery and K. Hewson, *J. Med. Chem.*, 11, 48 (1968).