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PART XVIII. 9-(3-DEOXY-3-FLUORO-β-D-XYLOFURANOSYL)ADENINE AND 9-(3-DEOXY-3-FLUORO-α-D-ARABINOFURANOSYL)ADENINE

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ABSTRACT

An alternative synthesis of 3-deoxy-3-fluoro-α-D-xylose (**4a**) from methyl 2,3-anhydro-5-*O*-benzyl-β-D-ribofuranoside (**1**) is described. Methyl 5-*O*-benzyl-3-deoxy-3-fluoro-β-D-xylofuranoside (**3**) and methyl 5-*O*-benzyl-3-deoxy-3-fluoro-α-D-arabinofuranoside (**11**) were converted, *via* the 2,5-di-*O*-benzoyl derivatives (**6**) and (**12**), into the corresponding αβ-D-glycosyl bromides (**7**) and (**13**). The latter compounds were then condensed with 6-benzamidopurine to yield the fluorinated nucleosides, 6-benzamido-9-(2,5-di-*O*-benzoyl-3-deoxy-3-fluoro-β-D-xylofuranosyl)purine (**8**) and 6-benzamido-9-(2,5-di-*O*-benzoyl-3-deoxy-3-fluoro-α-D-arabinofuranosyl)purine (**14**), respectively. Structural assignments of the fluoronucleosides (**8**) and (**14**) were based upon u.v. comparison with known 9-(3-deoxy-β-D-pentofuranosyl)adenines, and the fact that, on alkaline hydrolysis, compounds **8** and **14** yielded crystalline fluoronucleosides (**9**) and (**15**) which gave the 5′-toluene-*p*-sulphonates **10** and **16**; on heating, compound **10** formed a 3,5′-cyclic *p*-toluenesulphonate, whereas compound **16** did not. These results are consistent with the anomeric configuration assigned to 9-(3-deoxy-3-fluoro-β-D-xylofuranosyl)adenine (**9**) and 9-(3-deoxy-3-fluoro-α-D-arabinofuranosyl)adenine (**15**).

This synthesis of deoxyfluoronucleosides is considered to be less limited in application than those so far reported.

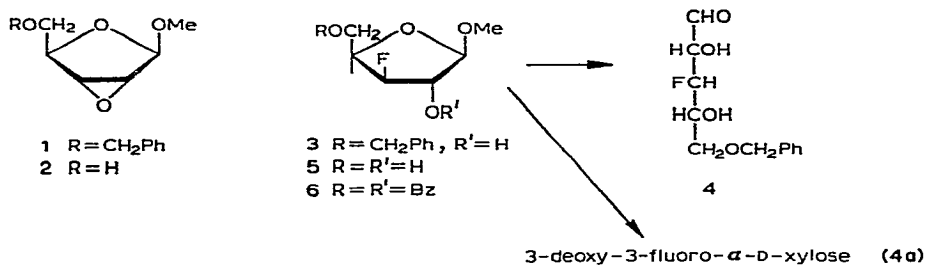
INTRODUCTION

Work so far reported on the introduction of fluorine into nucleosides has been based on (*i*) replacement of hydrogen by fluorine in the heterocyclic moiety (*e.g.*, 2-fluoroadenosine[1] and 5-fluorouridine[2]), or (*ii*) the replacement of the 2′-hydroxyl group of the nucleoside directly by fluorine (*e.g.*, 2′-deoxy-2′-fluorouridine[3]). As part of a synthetic programme directed towards the replacement of hydroxyl groups by fluorine, we now report the synthesis of 9-(3-deoxy-3-fluoro-β-D-xylofuranosyl)-adenine (**9**) and 9-(3-deoxy-3-fluoro-α-D-arabinofuranosyl)adenine (**15**).

RESULTS AND DISCUSSION

The method of introducing fluorine into the 2′-position of uridine by Fox *et al.*[3] appears to be limited to pyrimidines having an oxygen function at the 2-position

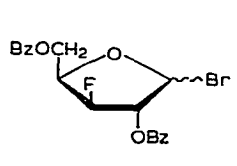
of the heterocycle. The use of suitably substituted deoxyfluoroglycosyl halides and their subsequent conversion into the nucleoside by established procedures, however, does not possess this limitation. In the pentose series, both 3-deoxy-3-fluoro-α-D-xylose and 3-deoxy-3-fluoro-β-D-arabinose are now available[4a], and we have, therefore, used these compounds as models for fluoronucleoside synthesis. 3-Deoxy-3-fluoro-αβ-D-xylose was previously synthesised by us from methyl 2,3-anhydro-4-*O*-benzyl-β-D-ribopyranoside[4a]. In order to utilise the furanose form of the carbohydrate, we have now synthesised this fluoro sugar by the action of potassium hydrogen fluoride (KHF_2) on methyl 2,3-anhydro-5-*O*-benzyl-β-D-ribofuranoside (**1**), obtained by benzylation of methyl 2,3-anhydro-β-D-ribofuranoside[5] (**2**). Acid hydrolysis of the resulting fluorohydrin **3** produced from compound **1** gave a reducing sugar **4** which consumed periodate (1 mole/mole) and liberated formic acid (1 mole/mole). These results are consistent with the 3-deoxy-3-fluoro-D-xylofuranose structure for compound **3**. Moreover, catalytic hydrogenation of compound **3**, followed by acid hydrolysis, gave a free deoxyfluoro sugar identical with crystalline[4b] 3-deoxy-3-fluoro-α-D-xylose (**4a**).



Catalytic hydrogenation of compound **3** gave the glycoside **5** which, on benzoyl ation, yielded methyl 2,5-di-*O*-benzoyl-3-deoxy-3-fluoro-β-D-xylofuranoside (**6**). Treatment of compound **6** with hydrogen bromide in glacial acetic acid gave the αβ-glycosyl bromides (**7**) which were immediately condensed with 6-benzamidopurine[6]. This reaction was carried out by two established methods: (*a*) with the 6-benzamidopurine as a chloromercuri salt[6], and (*b*) using nitromethane in the presence of mercuric cyanide[7]. The latter method gave better yields of a nucleoside which was assigned the 9-(3-deoxy-3-fluoro-β-D-xylofuranosyl) configuration (**8**), on the basis of ultraviolet comparison with 9-(3-deoxy-β-D-pentofuranosyl)adenines[8], the Trans Rule for nucleoside formation[9], and the fact that alkaline hydrolysis of **8** yielded a crystalline nucleoside (**9**) which gave a 5′-toluene-*p*-sulphonate (**10**) (this exchanged with sodium iodide in acetone in accordance with Oldham and Rutherford's rule[10]) that could be quaternized at N-3 of the purine on heating. The formation of this 3,5′-cyclo salt is in agreement with results reported by various workers[11] and indicates a β-D-configuration at the anomeric centres of compounds **8** and **9**.

A similar sequence of reactions was then applied to methyl 5-*O*-benzyl-3-deoxy-3-fluoro-α-D-arabinofuranoside[4a] (**11**), which was converted, *via* the 3,5-di-*O*-benzoyl derivative (**12**), into the αβ-glycosyl bromides (**13**). Condensation of **13** with

6-benzamidopurine by methods (*a*) or (*b*) gave a major nucleoside component which was assigned the 9-(3-deoxy-3-fluoro-α-D-arabinofuranosyl) configuration (**14**). This configuration was based on criteria already described for compound **8**. Confirmation



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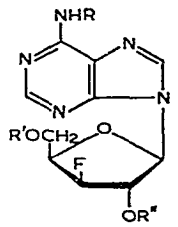
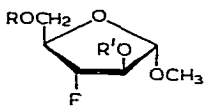
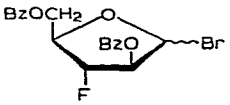


8 R = R' = R" = Bz
9 R = R' = R" = H
10 R = H, R' = Ts, R" = H



11 R = CH_2Ph, R' = H
12 R = R' = Bz



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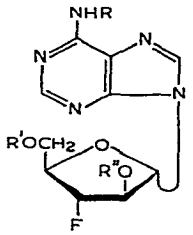

14 R = R' = R" = Bz
15 R = R' = R" = H
16 R = H, R' = Ts, R" = H

of the α-D-configuration of compound **14** was obtained by its alkaline hydrolysis to yield the crystalline nucleoside **15** which gave a 5′-toluene-*p*-sulphonate (**16**) that did not quaternize to a 3,5′-cyclic compound on heating.

EXPERIMENTAL

Melting points were determined with an Electrothermal apparatus and are uncorrected. Paper chromatography was performed as previously described[4a]. Thin-layer chromatography (t.l.c.) was carried out with Silica-gel G for carbohydrates and Silica Gel PF254 for nucleosides and purine bases. Carbohydrates were detected by spraying with sulphuric acid–ethanol (1:1) and heating for 10 min at 120°, and nucleosides and bases by viewing the plates under u.v. illumination. Preparative t.l.c. (p.l.c.) was performed as before[4a]. The solvent systems used were light petroleum (b.p. 40–60°)–ethyl acetate, 2:1 (*A*), 1:1 (*B*), acetone–ethyl acetate[8], 1:1 (*C*), and chloroform–methanol[12], 4:1 (*D*).

Microanalyses and fluorine determinations were performed by Drs. Weiler and Strauss, Oxford.

Methyl 2,3-anhydro-5-O-benzyl-β-D-ribofuranoside (**1**). — To methyl 2,3-anhydro-β-D-ribofuranoside[5] (**2**) (5.0 g) in anhydrous *N,N*-dimethylformamide (25 ml) were added silver oxide (7.0 g) and benzyl bromide (6 ml). The mixture was shaken for 24 h at room temperature and then diluted with chloroform (250 ml) and water (250 ml). The chloroform layer was separated and filtered, pyridine (30 ml)

was added, and the solution was washed successively with water (6 × 100 ml), 2M hydrochloric acid (3 × 100 ml), saturated aqueous sodium hydrogen carbonate (100 ml), and water (100 ml). The chloroform extract was dried ($MgSO_4$), and evaporated to dryness, and the resulting light-brown oil was distilled to give the product as a colourless oil (6.4 g), b.p. 130° (bath)/0.01 mm, $[\alpha]_D^{24}$ −90.8° (*c* 1.4, chloroform) (Found C, 66.7; H, 6.9. $C_{13}H_{16}O_4$ calc.: C, 66.1; H, 6.8%).

Methyl 5-O-benzyl-3-deoxy-3-fluoro-β-D-xylofuranoside (**3**). — A solution of methyl 2,3-anhydro-5-*O*-benzyl-β-D-ribofuranoside (**1**) (3.0 g) and KHF_2 (6.0 g) in ethane-1,2-diol (60 ml) was refluxed gently for 1.5 h. When cool, the solution was poured into saturated aqueous sodium hydrogen carbonate (500 ml) with stirring, and extracted with chloroform (3 × 100 ml); the extract was then dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The resulting syrup on t.l.c. (solvent *B*) contained two major components, R_F 0.4 and 0.6 (starting material). The mixture was resolved by p.l.c. (2 elutions with solvent *A*) to yield a fluorine-containing syrup (**3**) (1.1 g), $[\alpha]_D^{20}$ −62.0° (*c* 1.0, chloroform), which had i.r. absorption bands at 3440 (OH) and 1100–1000 cm^{-1} (C–F). (Found: C, 60.8; H, 6.9; F, 7.1. $C_{13}H_{17}FO_4$ calc.: C, 61.0; H, 6.6; F, 7.4%).

5-O-Benzyl-3-deoxy-3-fluoro-αβ-D-xylose (**4**). — Methyl 5-*O*-benzyl-3-deoxy-3-fluoro-β-D-xylofuranoside (**3**) (1.0 g) was dissolved in a mixture of *p*-dioxane (50 ml) and 0.25M sulphuric acid (50 ml), and the solution was refluxed for 3 h. The cooled solution was neutralized with barium carbonate, filtered, and evaporated to dryness *in vacuo*. The residue was taken up in absolute ethanol and filtered, and the filtrate was evaporated to dryness *in vacuo*, to yield a viscous, colourless, reducing syrup (**4**) (740 mg), R_F 0.26 (solvent *B*), $[\alpha]_D^{20}$ −2.5° (*c* 1.1, ethanol) (Found: C, 59.2; H, 6.3; F, 7.5. $C_{12}H_{15}FO_4$ calc.: C, 59.5; H, 6.2; F, 7.8%).

Periodate oxidation of 5-O-benzyl-3-deoxy-3-fluoro-αβ-D-xylose. — 5-*O*-Benzyl-3-deoxy-3-fluoro-αβ-D-xylose (**4**) (102.1 mg) was dissolved in water (20 ml) and 0.05M sodium metaperiodate (20 ml). At intervals, 2-ml portions were withdrawn, and the periodate consumed and acid liberated were determined as previously described[4a]. The results were as follows:

Time (min)	2	15	30	45	24 h
Periodate consumed (moles/mole)	0.97	0.94	0.98	1.01	1.01
Acid liberated (moles/mole)	0.80	0.85	0.90	0.90	0.93

The acid liberated was identified as formic acid by reduction to formaldehyde and characterisation with chromotropic acid[13].

Methyl 3-deoxy-3-fluoro-β-D-xyloside (**5**). — Methyl 5-*O*-benzyl-3-deoxy-3-fluoro-β-D-xylofuranoside (**3**) (1.0 g) in ethanol (25 ml) containing 5% palladium-on-charcoal (1.0 g) was hydrogenated at room temperature and atmospheric pressure until the uptake of hydrogen ceased (1 mole, 30 min). After filtration, the solution was evaporated to yield compound **5** as a viscous, non-reducing syrup, R_F 0.12 (solvent *B*), $[\alpha]_D^{20}$ −63.0° (*c* 1.6, ethanol) (Found: C, 43.2; H, 6.8; F, 11.2. $C_6H_{11}FO_4$ calc.: C, 43.4; H, 6.6; F, 11.4%). The glycoside was characterised as the

2,5-dibenzoate (**6**), m.p. 67°, $[\alpha]_D^{22}$ −22.0° (*c* 1.1, ethanol) (Found: C, 64.4; H, 5.2; F, 5.4. $C_{20}H_{19}FO_6$ calc.: C, 64.1; H, 5.1; F, 5.1%).

*3-Deoxy-3-fluoro-α-*D*-xylose* (**4a**). — Methyl 3-deoxy-3-fluoro-β-D-xylofuranoside (**5**) (0.50 g) was treated with refluxing 0.05M sulphuric acid (50 ml) for 1 h. The cooled solution was neutralized with barium carbonate, and the filtered solution was evaporated to dryness *in vacuo*. The residue was taken up in absolute ethanol, and the filtered solution was evaporated to dryness, yielding 3-deoxy-3-fluoro-αβ-D-xylose as a colourless, reducing syrup (0.401 g). This crystallized upon seeding with authentic compound **4a**, and was recrystallized from ethanol; m.p. 126–128°, $[\alpha]_D^{25}$ +75.3 → +25.7° (1 h) (*c* 1.7, water) (Found: C, 39.6; H, 6.2; F, 12.0. $C_5H_9FO_4$ calc.: C, 39.5; H, 5.9; F, 12.5%).

6-*Benzamido-9-(2,5-di-*O*-benzoyl-3-deoxy-3-fluoro-β-*D*-xylofuranosyl)purine* (**8**). — Methyl 2,5-di-*O*-benzoyl-3-deoxy-3-fluoro-β-D-xylofuranoside (**6**) (1.0 g) was dissolved in glacial acetic acid (10 ml) containing 2% of acetic anhydride. A solution of hydrogen bromide in glacial acetic acid (10 ml, 45% w/v) was added, and the resulting yellow solution was kept for 3 h at room temperature, and then evaporated to dryness *in vacuo* (< 30°). Residual hydrogen bromide and acetic acid were removed by three evaporations with anhydrous benzene. 2,5-Di-*O*-benzoyl-3-deoxy-3-fluoro-αβ-D-xylofuranosyl bromide (**7**) was obtained as a yellow syrup that was used immediately for the next step.

Method (*a*). A suspension of chloromercuri-6-benzamidopurine[6] (1.270 g) in xylene (100 ml, A.R.) was dried by slow azeotropic distillation of *ca.* 25 ml. The suspension was cooled to near room temperature, and a solution of compound **7** (prepared from 1.0 g of the glycoside **6**), in xylene (10 ml) was added. The suspension was refluxed under anhydrous conditions for 2 h. While hot, the suspension was rapidly filtered, and light petroleum (200 ml; b.p. 40–60°) was added to the filtrate. After being cooled to room temperature and storage for 1 h, the white flocculent precipitate was collected by filtration, and washed with light petroleum. The dried solid was dissolved in chloroform (50 ml) and the solution was washed with 30% aqueous potassium iodide (3 × 30 ml) and water (30 ml), and then dried ($MgSO_4$). Evaporation of the solution to dryness *in vacuo* gave a yellow, glassy solid, shown by t.l.c. (solvent *C*) to be a mixture of four components, including the two starting materials. Resolution of the mixture was accomplished by using p.l.c (solvent *C*), and the major product (R_F 0.68) was recovered by extraction with ethyl acetate. Evaporation of the extract to dryness gave compound **8** (0.80 g) as a chromatographically pure, pale-yellow glass, $[\alpha]_D^{21}$ −46.6° (*c* 0.8, chloroform), λ_{max} 231 (ε 35,200) and 279.5 nm (ε 18,800). (Found: C, 63.4; H, 4.5; N, 11.6; F, 3.4. $C_{31}H_{24}FN_5O_6$ calc.: C, 64.0; H, 4.1; N, 12.0; F, 3.3).

Method (*b*)[7]. A suspension of 6-benzamidopurine[6] (0.640 g) in nitromethane (40 ml) was dried by azeotropic distillation of *ca.* 10 ml of the solvent, during which most of the solid dissolved. To the warm suspension was added a solution of compound **7** (prepared from 1.0 g of the glycoside **6**) in nitromethane (5 ml), and finely powdered mercuric cyanide (1.0 g). The suspension was refluxed for 1 h,

dissolution being complete in this time. The solution was evaporated to dryness *in vacuo*, and the residue was suspended in chloroform (100 ml). After being washed with 30% aqueous potassium iodide (2 × 30 ml) and water (30 ml), the solution was dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The product, a colourless glass, was identical on t.l.c. to the mixture obtained by procedure (*a*), and was similarly resolved, to give compound **8** (0.85 g), which was identical in all respects to that obtained by procedure (*a*).

6-Benzamido-9-(2,5-di-O-benzoyl-3-deoxy-3-fluoro-α-D-arabinofuranosyl)purine (**14**). — Methyl 5-*O*-benzyl-3-deoxy-3-fluoro-α-D-arabinofuranoside (**11**) was converted into methyl 2,5-di-*O*-benzoyl-3-deoxy-3-fluoro-α-D-arabinofuranoside (**12**) as previously described[4a]. Treatment of compound **12** with hydrogen bromide in acetic acid, as detailed above, gave 2,5-di-*O*-benzoyl-3-deoxy-3-fluoro-αβ-D-arabinofuranosyl bromide (**13**) as a yellow gum that was used without further characterisation.

When procedures (*a*) and (*b*) were applied to compound **13**, compound **14**, in yields of 60% and 65%, respectively, was obtained as a glass, $[\alpha]_D^{21}$ +58.2° (*c* 0.8, chloroform), R_F 0.66 (solvent *C*), λ_{max} 230.5 (ε 28,800) and 279.5 nm (ε 16,700) (Found: C, 63.2; H, 4.6; N, 11.8; F, 3.2. $C_{31}H_{24}FN_5O_6$ calc.: C, 64.0; H, 4.1; N, 12.0; F, 3.3%).

9-(3-Deoxy-3-fluoro-β-D-xylofuranosyl)adenine (**9**). — A solution of 6-benzamido-9-(2,5-di-*O*-benzoyl-3-deoxy-3-fluoro-β-D-xylofuranosyl)purine (**8**) (58 mg) in 0.05N methanolic sodium methoxide (2 ml) was refluxed for 1 h, and then evaporated to dryness *in vacuo*. The residue was dissolved in water (2 ml) and neutralized with 2N acetic acid. Methyl benzoate was removed by washing with chloroform (3 × 1 ml), and the aqueous layer was evaporated to dryness *in vacuo*. The brown, gummy residue was readily crystallized from water to give compound **9** as colourless needles, m.p. 218–220°, R_F 0.22 (solvent *D*), $[\alpha]_D^{21}$ −40.1° (*c* 0.5, water), $\lambda_{max}^{H_2O,\ pH7}$ 259.5 nm (ε 13,300) (Found: C, 37.3; H, 5.7; N, 21.4; F, 6.3. $C_{10}H_{12}FN_5O_3 \cdot 3H_2O$ calc. C, 37.2; H, 5.6; N, 21.6; F, 5.9%). Karl Fischer analysis confirmed the presence of water of crystallization.

9-(3-Deoxy-3-fluoro-α-D-arabinofuranosyl)adenine (**15**). — By a similar procedure to that described above, 6-benzamido-9-(2,5-di-*O*-benzoyl-3-deoxy-3-fluoro-α-D-arabinofuranosyl)purine (**14**) was hydrolysed, giving compound **15** as colourless needles, m.p. 133–135°, R_F 0.25 (solvent *D*), $[\alpha]_D^{22}$ +64.2° (*c* 0.5, water), $\lambda_{max}^{H_2O,\ pH7}$ 259 nm (ε 14,500) (Found: C, 42.5; H, 4.8; N, 24.5; F, 7.0. $C_{10}H_{12}FN_5O_3.H_2O$ calc.: C, 41.8; H, 4.9; N, 24.4; F, 6.6%). Karl Fischer analysis confirmed the presence of water of crystallization.

9-(3-Deoxy-3-fluoro-5-O-tosyl-β-D-xylofuranosyl)adenine* (**10**). — 9-(3-Deoxy-3-fluoro-β-D-xylofuranosyl)adenine (**9**) (101 mg) was dissolved in anhydrous pyridine (2 ml) and cooled in ice. Toluene-*p*-sulphonyl chloride (165 mg) was added, and the solution was kept for 24 h at room temperature and then poured into water (20 ml). The product was extracted with chloroform (3 × 15 ml), and the extract was washed

*Tosyl = toluene-*p*-sulphonyl.

with saturated aqueous sodium hydrogen carbonate (2 × 20 ml) and water (20 ml), dried ($MgSO_4$), and evaporated to dryness *in vacuo*. On cooling, the residue solidified. T.l.c. (solvent *D*) showed the presence of one major component, R_F 0.60, and small proportions of compounds having R_F 0.68 and 0.75. The major component, an amorphous solid (51 mg), which proved to be the title compound **10**, was isolated by p.l.c. (solvent *D*). It had λ_{max}^{EtOH} 261 nm (ε 12,800) (Found: C, 48.4; H, 4.6. $C_{17}H_{18}FN_5O_5S$ calc.: C, 48.2; H, 4.3%). Bands in the i.r. spectrum at 1175 and 1365 cm^{-1} indicated the presence of the sulphonyloxy residue. On refluxing sulphonate **10** (47 mg) with sodium iodide (33 mg) in anhydrous acetone (0.35 ml), sodium toluene-*p*-sulphonate was deposited.

9-(3-Deoxy-3-fluoro-5-O-tosyl-α-D-arabinofuranosyl)adenine (**16**). — Toluene-*p*-sulphonylation of compound **15**, as described above, gave the title compound as an amorphous solid, R_F 0.60 (solvent *D*), λ_{max}^{EtOH} 261 nm (ε 7550). The i.r. spectrum contained bands at 1180 and 1365 cm^{-1} ($-SO_2R$), and the sulphonyloxy group of compound **16** exchanged with sodium iodide–acetone in accordance with Oldham and Rutherford's rule[10].

3,5'-Cyclo-9-(3-deoxy-3-fluoro-β-D-xylofuranosyl)adenine toluene-p-*sulphonate.* — 9-(3-Deoxy-3-fluoro-5-*O*-tosyl-β-D-xylofuranosyl)adenine (37 mg) was dissolved in anhydrous *p*-dioxane[11b] (3 ml) and the solution was refluxed for 3 h. A white solid separated. The solvent was evaporated, and the residue was re-suspended in acetone. The solid was filtered off, and washed with acetone. The acetone-soluble material was shown (t.l.c.) to be starting material, and the insoluble portion (15 mg), on the basis of t.l.c. [2 spots, R_F 0.02, 0.21 (toluene-*p*-sulphonate anion), solvent *D*] and u.v. spectrum [$\lambda_{max}^{H_2O\,(pH7)}$ 274 nm (ε 10,900)], was assigned the structure of the title compound. The appearance of intense bands in the i.r. spectrum at 1215 and 684 cm^{-1}, assigned to the toluene-*p*-sulphonate anion, provided further evidence for this structure.

9-(3-Deoxy-3-fluoro-5-*O*-tosyl-α-D-arabinofuranosyl)adenine underwent no change on similar treatment, and therefore possessed the α-D-configuration at the anomeric centre.

ACKNOWLEDGMENTS

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