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Studies of Nucleosides and Nucleotides. XLIX.[1] Synthesis of 8-Fluoroadenosine[2]

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In order to obtain 8-fluoroadenosine, 8-aminoadenosine was subjected to Schiemann reaction. However, presumably due to lability of the nucleosidic linkage of 8-fluoroadenosine, only 8-fluoroadenine and 8-oxyadenine were obtained as the product.

When 2′,3′,5′-tri-O-acetyl-8-aminoadenosine, which was synthesized from 2′,3′,5′-tri-O-acetyl-8-bromoadenosine by way of 8-azido compound, was diazotized with sodium nitrite in 40% HBF_4 at −20°, 2′,3′,5′-tri-O-acetyl-8-fluoroadenosine was obtained in yield around 10%. Optical properties and migratory behaviors in paper chromatography resembled those of 8-bromoadenosine derivative. 8-Fluoroinosine and 8-oxyadenine were also obtained as the byproduct.

Deacetylation of triacetyl-8-fluoroadenosine gave 8-fluoroadenosine, which had circular dichroism (CD) profile similar to that of 8-bromoadenosine and a *syn* conformation was suggested to this compound.

8-Aminoguanosine gave 8-aminoxanthine and 8-fluoroxanthine by the Schiemann reaction.

In recent years, a number of 8-substituted purine nucleosides[4–8] has been synthesized and some of these compounds had anti-tumor and anti-viral activity.[8,9] Especially 8-halogenopurine nucleosides are useful intermediates for the synthesis of cyclonucleosides.[10]

Nucleosides having fluorine are important in the pyridimine series, because 5-fluoro and 5-trifluoromethyl derivatives were reported to be active against cancer cells and viruses.[11–13] In the purine nucleoside series 2-fluoroadenosine was synthesized by Montgomery, *et al.*[14] and an antibiotic nucleosidin[15] had a fluorine atom at C-4′ position of the carbohydrate moiety of adenosine. If we compare pyrimidine and purine nucleosides in the hydrogen bonded structure of Watson–Crick sense,[16] C-5 of the pyrimidine and C-8 of the purine seem to be the equivalent position which is not involved in the hydrogen bonding site. From this point of view, we attempted to synthesize 8-fluoroadenosine and guanosine starting from naturally occurring nucleosides.

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The substitution of halogeno compounds to the fluoro derivative using metal fluoride was achieved in the heterocyclic base[17] involving purine[18] and pyrimidine.[19] We started therefore with 8-bromoadenosine (I) and 8-bromoguanosine, which are easily accessible in our laboratory. These compounds were allowed to react with AgF, KF and NaF in various solvents and conditions. However, we could not isolate 8-fluoro nucleosides from the reaction mixture, which consisted of a complex mixture of the products. The replacement of 8-iodoadenosine (III), which has readily leaving 8-substituent and could be synthesized *via* 8-mercaptoadenosine (II), has also failed. When the 2′,3′,5′-tri-O-acetyl protected nucleosides, IV and V were used, none of the desired product were obtained.

We investigated next the application of Schiemann reaction[20] to 8-aminoadenosine (VIIa). Montgomery, *et al.*[14] synthesized 2-fluoroadenosine from 2-aminoadenosine using 40% fluoroboric acid and sodium nitrite in the relatively low yield. In this case a selective diazotization of 2-amino group prior to that at 6-position occurred. When 8-aminoadenosine[7] (VIIa) was treated with sodium nitrite in 40% fluoroboric acid at −20° for 20 min, two compounds appeared at *Rf* 0.54 and *Rf* 0.32 on a paper chromatogram. The substance having *Rf* 0.32 was identified as 8-oxyadenine (IX) by the comparison of its *Rf* value and ultraviolet (UV) absorption properties with an authentic sample.[21] The substance having *Rf* 0.54, which obtained in relatively low yield, had UV absorption maxima at 266 nm (in acid) and 270 nm (neutral and alkali), which resembled those of 8-bromoadenine.[22] From the difference in *Rf* values with 8-bromoadenine this compound has been assigned to 8-fluoroadenine (VIII). Since 8-aminoadenosine (VIIa) is stable in 40% HBF_4 solution at −20° and 8-oxyadenosine is resistant to the acidic hydrolysis,[23] it could be deduced that 8-amino group in VIIa had been diazotized first, replaced by fluorine, and 8-fluoroadenine (VIII) resulted by the acidic hydrolysis. 8-Fluoroadenine, thus obtained, could be easily hydrolyzed to afford 8-oxyadenine (IX). Therefore it might be ovbious that 8-amino group was first diazotized prior to 6-amino group. If we assume the protonation at N^1 and delocalization of + charge both to N^1 and N^6, 8-amino group could be diazotized prior to 6-amino group.

In order to avoid this cleavage of the nucleosidic linkage, acetylation of compound I was investigated, because stabilization of the nucleosidic linkage by the protection of sugar OH group was reported.[24] When compound VIIa was acetylated in pyridine using acetic anhydride, 2′,3′,5′-O-8-N-tetraacetyl-8-aminoadenosine was obtained. To limit the acetylation only to the sugar OH, compound VIIa was treated with acetic anhydride in 4N sodium hydroxide at pH 7.[25] Although 2′,3′,5′-tri-O-acetyl-8-aminoadenosine (VIIb) was obtained in a yield of 20%, compound having acetyl group on 8-amino accompanied. We therefore treated 8-azidoadenosine (VIa) with acetic anhydride in pyridine and obtained 2′,3′,5′-tri-O-acetyl-8-azidoadenosine (VIb) in a yield of 75%. The structure of VIb was confirmed by UV absorption properties identical with those of 8-azidoadenosine,[7] infrared (IR) absorption band at 2160 cm^{-1} ascribed to $-N_3$, resistance for metaperiodate oxidation on paper chromatogram,[26] and elemental analysis. Compound VIb was hydrogenated with palladium charcoal as catalyst to give 2′,3′,5′-tri-O-acetyl-8-aminoadenosine (VIIb) in a yield of 69%. Compound VIIb could be converted to 8-aminoadenosine (VIIa) by the treatment with methanolic ammonia and the structure was confirmed.

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When compound VIIb was dissolved in 40% fluoroboric acid at −20° and diazotized with three equivalents of sodium nitrite, a colorless glass was obtained. Recrystallization of this material from benzene gave a colorless needles having mp 170—171°. This compound (X) had UV absorption maxima at 261.5 nm in acidic, 263 nm in neutral and 264 nm in alkaline solution, which closely resembled those of 8-bromoadenosine. In nuclear magnetic resonance (NMR) spectra a singlet peak at 7.48 δ, which was assigned to 6-NH_2, appeared and a peak corresponding to 8-NH_2 group disappeared. A proton of position 2 appeared at 8.18 δ and that of 8-H was not found. Elemental analysis also supported the structure of 2′,3′,5′-tri-O-acetyl-8-fluoroadenosine for the compound X. In order to confirm the replacement of 8-amino to 8-fluoro atom, compound X was subjected to the reaction with NaSH in DMF. By this treatment a characteristic change of absorption maxima at 264 nm to 300 nm occurred. The resulting 8-mercapto derivative was further deacylated to give 8-mercaptoadenosine, which was identical with a sample derived from 8-bromoadenosine.

From the chloroform layer, a small amount of product having $\lambda_{\max}^{H^+}$ 275 nm, $\lambda_{\max}^{H_2O}$ 259 nm and $\lambda_{\max}^{OH^-}$ 260 nm was found by thin-layer chromatography (TLC). From the UV absorption and other properties this compound was thought to be 2,′3′,5′-tri-O-acetyl-8-fluoroinosine (XI). This assignment was confirmed by the conversion of triacetyl-8-fluoroadenosine (X) to XI by the treatment with sodium nitrite in acetic acid. From the water layer of the above extraction 8-oxyadenine was also found. These facts suggested that once protected 8-fluoroadenosine was formed, it was susceptible to the deamination with nitrous acid and gave 8-fluoroinosine derivative. However, if the nucleosidic linkage of compound X was cleaved prior to the deamination, 8-fluoroadenine was hydrolyzed to give 8-oxyadenine.

Compound X was then deacylated with methanolic ammonia at room temperature for 24 hr. 8-Fluoroadenosine (XII) was obtained as needles having mp 190—191° in a quantitative yield. UV absorption properties of the compound XII were identical with those of the protected nucleoside (X). In paper chromatographies performed in several solvent systems, 8-fluoroadenosine (XII) had similar *Rf* values with 8-bromoadenosine. The final confirmation of the structure of XII was made by elemental analysis and circular dichroism (CD) spectra described later.

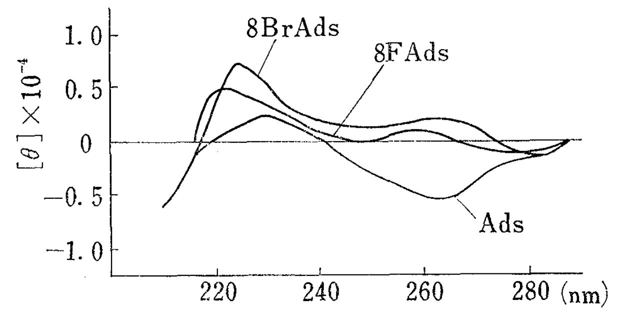

Fig. 1. Circular Dichroism of Adenosine, 8-Bromoadenosine and 8-Fluoroadenosine

Recently we have measured CD of various 8-substituted purine nucleosides[27] and found that 8-bromoadenosine existed in *syn* conformation in contrary to the ordinary nucleosides such as adenosine, which was found as having anti conformation.[28] The observation is consistent with Travale and Sobell's finding[29] that 8-bromoadenosine and 8-bromoguanosine were in the *syn* conformation in crystals. We therefore measured CD of 8-fluoroadenosine (XII). As shown in Fig. 1, compound XII has a negative Cotton band at around 280 nm and two positive bands at 258 and 223 nm. These profile closely resemble those of 8-bromoadenosine. We therefore postulated that 8-fluoroadenosine may exist in the *syn* conformation as in the case of 8-bromoadenosine. The reason why relatively small fluorine atom (1.35 Å in Van der Waals radii) exerted a big effect to the rotation of the base around nucleosidic linkage, remains to be elucidated by further investigations.

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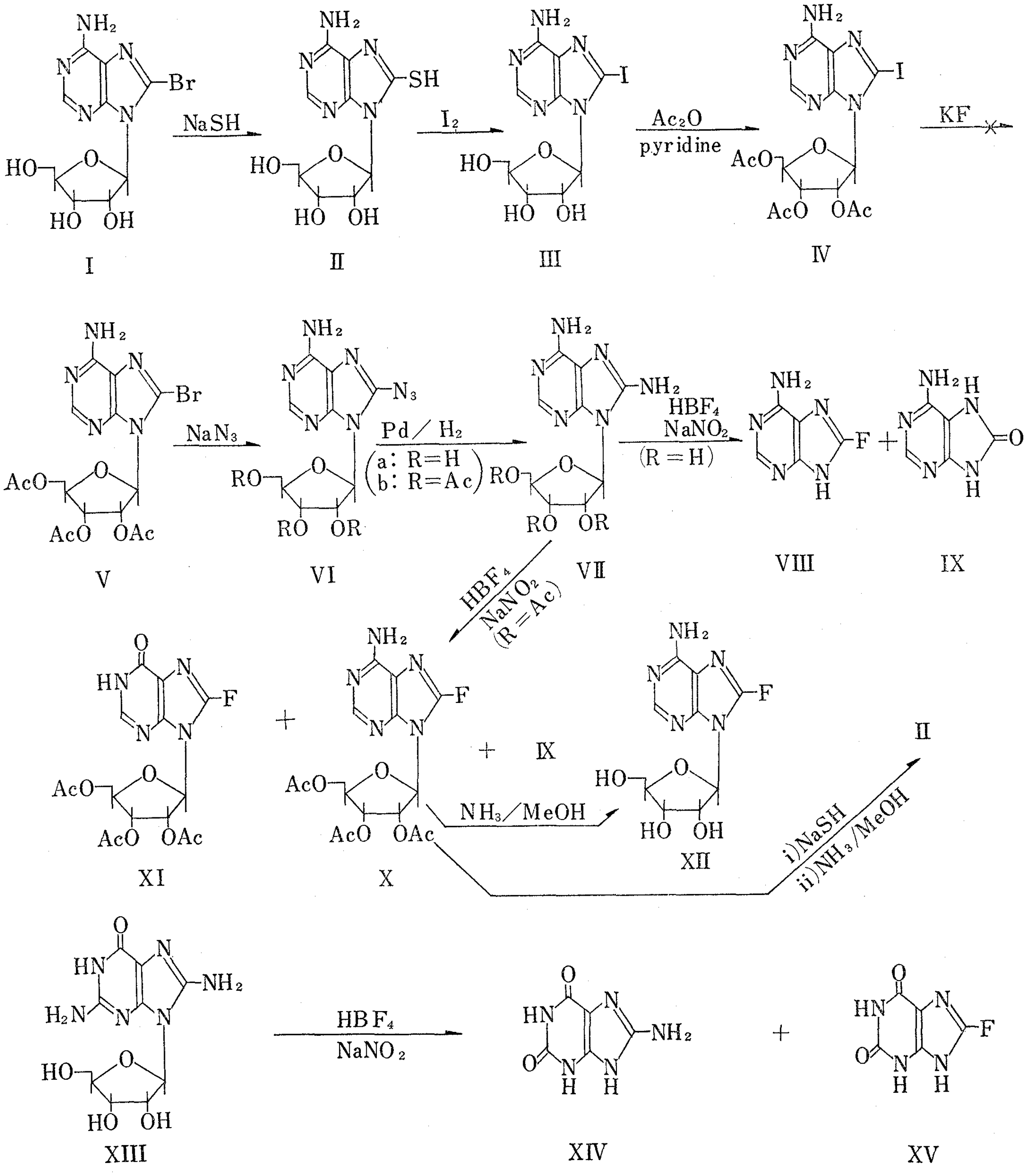

Chart 1

When the same type of Schiemann reaction was applied to 8-aminoguanosine (XIII), the product isolated was only 8-fluoroxanthine (XV) and 8-aminoxanthine (XIV). From this fact it was deduced that in compound XIII nucleosidic linkage was extremely labile to the acid and 2-amino group was diazotized prior to the 8-amino group. Furthermore, diazonium ion on 2-C atom was not stabilized sufficiently for the attack of fluoride and could easily be hydrolyzed. Several attempts to make suitably protected 8-aminoguanosine derivative were unsuccessful. This may imply that to more acidlabile deoxypurine nucleosides the Schiemann reaction is not applicable and other route must be chosen for the introduction of a fluoro atom to the position 8.

Experimental[30]

Paper Chromatography——Performed on Toyo filter paper 51A by ascending technique. Solvent systems used were: A, water adjusted to pH 10 with ammonia; B, butanol–water (86:14); C, isopropanol–ammonia–water (7:1:2).

2′,3′,5′-Tri-O-acetyl-8-bromoadenosine——8-Bromoadenosine[6,31] (3.47 g, 10 mmoles) was dissolved in pyridine (100 ml) and acetic anhydride (10 ml) was added into the solution. The reaction mixture was kept at room temperature for 10 hr and poured into ice–water (200 ml). Organic material was extracted with chloroform (200 ml), washed with aqueous bisulfite solution and water successively, and dried over sodium sulfate. Chloroform was evaporated in vacuo and the residue was recrystallized from ethanol (100 ml). Triacetyl-8-bromoadenosine was obtained as needles, mp 181° (4.12 g, 87%). *Anal.* Calcd. for $C_{10}H_{8}O_{8}N_{5}Br$: C, 40.71; H, 3.48; N, 14.87. Found: C, 40.80; H, 3.94; N, 14.83. UV: $\lambda_{\text{max}}^{\text{pH }2}$ 263 nm, $\lambda_{\text{max}}^{\text{pH }7}$ 265 nm, $\lambda_{\text{max}}^{\text{pH }12}$ 265.5 nm. TLC (solvent, chloroform–ethanol, 18:2) *Rf* 0.63.

8-Mercaptoadenosine——8-Bromoadenosine (2.72 g, 6.5 mmoles) was dissolved in dimethyl formamide (DMF 50 ml). To this solution was added 40% NaSH (2.7 ml, 19.5 mmoles) and the mixture was kept at room temperature for 10 hr. The solvent was removed by vaccum distillation and the residue was dissolved in water (50 ml). Neutralization with NaOH afforded a precipitate, which was filtered, washed and dried in a desiccator over P_2O_5. This material was recrystallized from water–ethanol mixture to give pale-yellow crystals, mp 170° (decomp.). Yield was 950 mg. *Anal.* Calcd. for $C_{10}H_{13}O_{4}N_{5}S$: C, 40.17; H, 4.38; N, 23.43. Found: C, 40.02; H, 4.66; N, 22.89. UV: $\lambda_{\text{max}}^{\text{pH }2}$ 222, 241, 308 nm; $\lambda_{\text{max}}^{\text{pH }7}$ 231, 299, 306 nm; $\lambda_{\text{max}}^{\text{pH }12}$ 229, 298 nm. PPC[32]: *Rf* (A) 0.50, *Rf* (B) 0.15, *Rf* (C) 0.35.

8-Iodoadenosine——8-Mercaptoadenosine (1 g, 3.4 mmole) was dissolved in water (100 ml) containing pottasium iodide (1.8 g, 10.8 mmoles) and the mixture was stirred at room temperature for 30 hr. Resulting precipitates were collected by filtration, washed with 40% potassium iodide solution (50 ml) and recrystallized from ethanol–water. 8-Iodoadenosine was obtained as slightly yellow crystals, mp 203—205° (yield 530 mg, 40.1%). *Anal.* Calcd. for $C_{10}H_{12}O_{4}N_{5}I$: C, 30.55; H, 3.08; N, 17.63. Found: C, 30.24; H, 2.87; N, 17.85. UV: $\lambda_{\text{max}}^{\text{pH }2}$ 271, 279 (shoulder) nm; $\lambda_{\text{max}}^{\text{pH }7}$ 219, 269 nm; $\lambda_{\text{max}}^{\text{pH }12}$ 267, 280 (shoulder) nm. PPC: *Rf* (A) 0.43; *Rf* (C) 0.60.

2′,3′,5′-Tri-O-acetyl-8-iodoadenosine——8-Iodoadenosine (1 g, 2.5 mmoles) was dissolved in pyridine (100 ml) and acetic anhydride (5 ml) was added into the solution. The mixture was stirred at room temperature for 10 hr. Ethanol (30 ml) was added into the solution and evaporated to give a residue. The residue was taken up in chloroform (100 ml), washed with 5% sodium bicarbonate solution, and chloroform was evaporated *in vacuo*. Residual glass was recrystallized from ethanol to give 1.11 g (84%) of acetyl-iodoadenosine, mp 208°. *Anal.* Calcd. for $C_{16}H_{18}O_{7}N_{5}I$: C, 36.99; H, 3.49; N, 13.48. Found: C, 36.96; H, 3.43; N, 13.26. UV: $\lambda_{\text{max}}^{\text{pH }2}$ 271, 279 (shoulder) nm; $\lambda_{\text{max}}^{\text{pH }7}$ 219, 269 nm; $\lambda_{\text{max}}^{\text{pH }12}$ 267, 280 (shoulder) nm. TLC ($CHCl_3$–ethanol, 35:5): *Rf* 0.67.

2′,3′,5′-Tri-O-acetyl-8-azidoadenosine——8-Azidoadenosine[7] (2.20 g, 7.1 mmoles) was dissolved in pyridine (200 ml) and acetic anhydride (15 ml) was added into the solution. The mixture was kept at room temperature for 10 hr. To the solution was added ethanol (100 ml) and the solution evaporated to dryness. The residue was taken up in chloroform, washed with 5% sodium bicarbonate and finally with water. Drying over sodium sulfate and evaporation of the solvent gave a colorless glass (2.40 g, 78%). *Anal.* Calcd. for $C_{16}H_{18}O_{7}N_{8}$: C, 44.37; H, 4.15; N, 25.42. Found: C, 43.88; H, 4.02; N, 24.91. UV: $\lambda_{\text{max}}^{\text{pH }2}$ 281 nm; $\lambda_{\text{max}}^{\text{pH }7}$ 281 nm; $\lambda_{\text{max}}^{\text{pH }12}$ 281 nm. IR: $\nu_{\text{max}}^{\text{Nujol}}$ 2160 cm^{-1} ($-N_3$). TLC ($CHCl_3$–EtOH, 35:5): *Rf* 0.81.

2′,3′,5′-Tri-O-acetyl-8-aminoadenosine——2′,3′,5′-Tri-O-acetyl-8-azidoadenosine (3.16 g, 7.3 mmoles) was dissolved in ethanol (100 ml) and hydrogenated in the presence of 10% palladium charcoal as catalyst. The catalyst was removed by filtration and washed with hot ethanol. Filtrate and washings were combined and evaporated *in vacuo*. The residue was dried *in vacuo* over P_2O_5. Triacetyl-aminoadenosine was obtained as a colorless glass (2.02 g, 69%). *Anal.* Calcd. for $C_{16}H_{20}O_{7}N_{6}$: C, 47.11; H, 4.91; N, 20.60. Found: C, 47.02; H, 4.65; N, 20.24. UV: $\lambda_{\text{max}}^{\text{pH }2}$ 271 nm; $\lambda_{\text{max}}^{\text{pH }7}$ 272 nm; $\lambda_{\text{max}}^{\text{pH }12}$ 272 nm. IR: band at 2160 cm^{-1} ($-N_3$) disappeared. TLC ($CHCl_3$–EtOH, 35:5): *Rf* 0.40.

Schiemann Reaction of 8-Aminoadenosine——8-Aminoadenosine (1 g, 3.58 mmoles) was dissolved in 40% HBF_4 (30 ml) at −15—−20°. Into this solution was added sodium nitrite (480 mg, 2 equivalents) and the stirring continued at −15° for 20 min. The mixture was adjusted to pH 6 with conc. ammonia with cautious maintaining of the temperature at −20°. After the temperature of the solution raised to room temperature, methanol (100 ml) was added. Resulting precipitate (inorganic salt) was filtered off and the filtrate

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30) UV absorption spectra were taken with a Hitachi EPS-3T recording spectrophotometer, IR spectra with a Hitachi EPI-L spectrophotometer, NMR with a Hitachi H-6013 high resolution spectrometer operated at 60 MHz, with tetramethylsilane as internal standard, and circular dichroism (CD) with a JASCO ORD/UV-5 spectropolarimeter with CD attachment.

31) M. Ikehara and M. Kaneko, *Tetrahedron*, **26**, 4251 (1970).

32) PPC stands for paper partition chromatography and *Rf*(A) for *Rf* value observed in solvent A.

was filtered again. The filterate was concentrated to a small balk and applied to a paper chromatography in solvent C. Two bands appeared at *Rf* 0.32 (main) and *Rf* 0.54.

Substance at *Rf* 0.32 was excized and eluted with water. UV: $\lambda_{max}^{pH\,2}$ 264, 280 nm; $\lambda_{max}^{pH\,7}$ 270 nm; $\lambda_{max}^{pH\,12}$ 280 nm. This spot could not be revealed by metaperiodate spray.[26] Cochromatography with an authentic sample of 8-oxyadenine showed their identity. Remaining reaction mixture was evaporated to a small balk and set aside for several days. A precipitate obtained by filtration (50 mg) showed *Rf*(C) 0.45 and UV absorption: $\lambda_{max}^{pH\,2}$ 266 nm; $\lambda_{max}^{pH\,7}$ 270 nm; $\lambda_{max}^{pH\,12}$ 270 nm, which resembled those of 8-bromoadenine. Cochromatography with 8-bromoadenine (*Rf* (C) 0.58) showed a slight difference.

2′,3′,5′-Tri-O-acetyl-8-fluoroadenosine——2′,3′,5′-Tri-O-acetyl-8-aminoadenosine (2.10 g) was dissolved in 40% HBF_4 (20 ml), which was previously cooled to −20° in a dry ice–acetone bath. After this solution was stirred for 5 min, sodium nitrite (1.10 g, 3 equivalents) in water (5 ml) was added dropwise during 5 min. The temperature of the mixture was strictly maintained at −20° and the stirring was continued for 20 min. The reaction mixture was cooled to −50° and methanol (300 ml) was added. The solution was adjusted to pH 7 with conc. ammonia at below −20°. After the temperature of the solution raised to room temperature, resulting inorganic salts were removed by filtration. The filtrate was evaporated *in vacuo* to dryness. The residue was shaken with chloroform (300 ml) and water (200 ml), and the organic layer was evaporated *in vacuo*. The residue was dissolved in ethyl acetate (30 ml) and applied to a column of alumina (Merck, Grade III). Elution with ethyl acetate gave fractions having *Rf* 0.28 in TLC (chloroform–ethanol, 37:3). Ethyl acetate was evaporated to give a pale yellow glass (561 mg, 29%). The glass was dissolved in benzene (10 ml) and kept at 10° overnight. Triacetyl-8-fluoroadenosine was obtained as fine needles, mp 170—171° (192 mg, 9.1%). *Anal.* Calcd. for $C_{16}H_{18}O_7N_5F \cdot H_2O$: C, 44.80; H, 4.69; N, 16.33. Found: C, 44.80; H, 4.03; N, 16.03. UV: $\lambda_{max}^{pH\,2}$ 2615 nm (ε 17200); $\lambda_{max}^{pH\,7}$ 263 nm (ε 14600); $\lambda_{max}^{pH\,12}$ nm (ε 15300). NMR: (in DMSO-d_6) 1.94, 2.10 δ (9H, $CH_3CO \times 3$); 4.28, 5.77, 6.09 δ (6H, 1′, 2′, 3′, 4′, and 5′-H); 7.48 δ (s, 2H, 6-NH_2, disappeared in D_2O); 8.18 δ (s, 1H, H-2). Coupling[33] of 1′-H with 8-F could not be detected. PPC: *Rf* (B) 0.86, *Rf* (C) 0.74.

8-Fluoroadenosine——2′,3′,5′-Tri-O-acetyl-8-fluoroadenosine (50 mg) was dissolved in methanol (10 ml), which was previously saturated with ammonia at 0°. The flask was stopped and kept at room temperature for 24 hr. Ammonia and methanol were carefully evaporated *in vacuo* and from the residual glass acetamide was removed by sublimation in 1mm Hg at 50°. A glass (30.3 mg) was recrystallized from 89% ethanol to give tiny needles, mp 190—191°. *Anal.* Calcd. for $C_{10}H_{12}O_4N_5F$: C, 42.24; H, 4.23; N, 24.58. Found: C, 41.92; H, 4.56; N, 24.31. UV: $\lambda_{max}^{pH\,2}$ 261.5 nm; $\lambda_{max}^{pH\,7}$ 263 nm; $\lambda_{max}^{pH\,12}$ 264 nm. PPC: *Rf* (A) 0.50, *Rf* (B) 0.51, *Rf* (C) 0.77.

Schiemann Reaction of 8-Aminoguanosine——8-Aminoguanosine (1 g) was dissolved in 40% HBF_4 at −20°. Into this solution was added sodium nitrite (480 mg, 2 equivalents) in water (1ml) with stirring at −20°. After 20 min, the mixture was brought to pH with dropwise addition of conc. ammonia. Resulting precipitates were collected by filtration and dissolved in methanol. Insoluble materials were filtered off and the filtrate was evaporated *in vacuo* to a glass. The glass was recrystallized from water to give a crystalline material (75 mg). UV: $\lambda_{max}^{pH\,2}$ 223, 280 nm; $\lambda_{max}^{pH\,7}$ 235 (shoulder), 288 nm; $\lambda_{max}^{pH\,12}$ 295 nm. PPC: *Rf* (B) 0.05, *Rf* (C) 0.09. From the UV absorption properties this compound was assigned to 8-aminoxanthine. As the second crop a substance having UV absorption properties: $\lambda_{max}^{pH\,2}$ 268 nm; $\lambda_{max}^{pH\,7}$ 270 nm; $\lambda_{max}^{pH\,12}$ 274 nm was obtained. *Rf* (B) 0.17. This compound was assigned to 8-fluoroxanthine, because it had UV absorption maxima which were slightly bathochromic than those of xanthine.[34]

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33) R.J. Cushley, I. Wempen and J.J. Fox, *J. Am. Chem. Soc.*, **90**, 706 (1968).
34) E. Chargaff and J.N. Davidson, "The Nucleic Acids," Vol 1, 1955, p. 502.