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The Preparation of 6-Fluoropurines by the Modified Schiemann Reaction (1)

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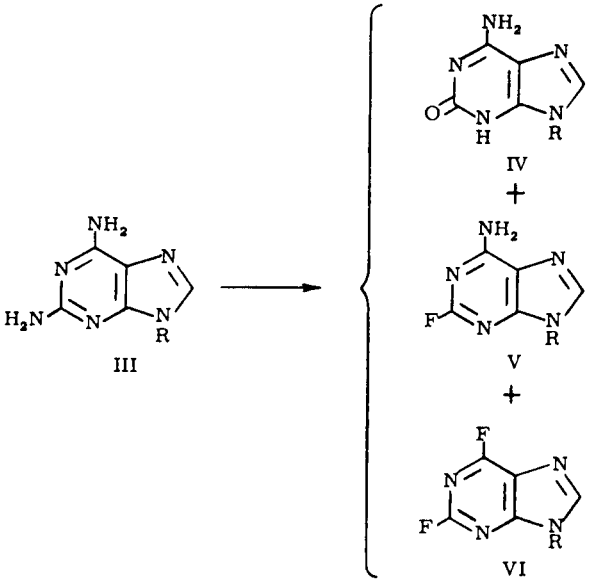
Sir:

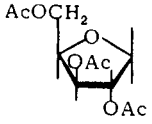
Adenine and its derivatives can be converted with difficulty into hypoxanthine (2) and the corresponding derivatives (3-6) by treatment with sodium nitrite in aqueous acid, or better, by treatment with nitrosyl chloride (5,7). Although these reactions presumably proceed by nitrosation of the amino group followed by attack of water on the diazonium salt, a number of investigators have reported the failure of adenines to undergo other normal diazotization-replacement reactions (8-12) that proceed by reaction of the diazonium or carbonium ion with anions rather than water. 2,6-Diaminopurine and its ribonucleoside react with sodium nitrite in aqueous acid to give isoguanine and crotonoside respectively (13), nitrosation occurring preferentially at the 2-amino group in both cases. The 2-amino group will also undergo other normal diazotization-replacement reactions, even though the yields are low (14-16). If the 2-amino group of 2,6-diamino-9-β-D-ribofuranosylpurine is blocked by acetylation, nitrosation can be forced to take place at the 6-amino group to give *N*-acetylguanosine (17).

In a study of the action of nitrous acid on a number of condensed 2,4-diaminopyrimidine ring systems, Trattner *et al.*, (18) found that in all cases, including 2,6-diaminopurine, nitrosation of the 2- but not the 6-amino group (19) took place giving the corresponding 2-hydroxy-6-aminoheterocycles. The results of these various studies have led investigators to conclude (20) that the modified Schiemann reaction (14) is limited to the synthesis of 2-fluoropurines, and this conclusion has been generally accepted. Despite the foregoing precedents, we now wish to report cases in which we have found that nucleosides of adenine and 2,6-diaminopurine do undergo a modified Schiemann reaction to give 6-fluoropurine nucleosides (21), compounds of potential biologic interest because of the high degree, broad-spectrum activity of 2-fluoroadenosine (14,22).

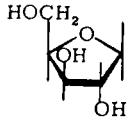
9-(2′,3′,5′-Tri-*O*-acetyl-β-D-xylofuranosyl)-2,6-dichloropurine (I), prepared by the fusion of 2,6-dichloropurine with 1,2,3,5-tetra-*O*-acetyl-D-xylofuranose (23,24), reacted with sodium azide to give a 94% yield of 9-(2′,3′,5′-tri-*O*-acetyl-β-D-xylofuranosyl)-2,6-diazidopurine (II), which was reduced catalytically (5% Pd/C) to 9-(2′,3′,5′-tri-*O*-acetyl-β-D-xylofuranosyl)-2,6-diaminopurine (IIIa) in 80% yield. Treatment of IIIa with sodium nitrite in 48% fluoboric acid gave a mixture from which 9-(2′,3′,5′-tri-*O*-acetyl-β-D-xylofuranosyl)isoguanine (IVa, 40%), 9-(2′,3′,5′-tri-*O*-acetyl-β-D-xylofuranosyl-2-fluoroadenine (Va, 13%), and 9-(2′,3′,5′-tri-*O*-acetyl-β-D-xylofuranosyl-2,6-difluoro-



a series: R =



b series: R =



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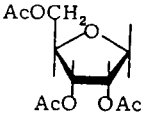
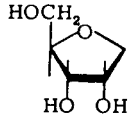


d series: R =



purine (VIa, 16%) were isolated. VIa was identified by its elemental analysis, its ultraviolet, infrared, and pmr spectra, and by its conversion to 2-fluoro-9-β-D-xylofuranosyladenine (Vb) by treatment with alcoholic ammonia.

By using the same sequence of reactions 2′,3′,5′-tri-*O*-acetyl-2-fluoroadenosine (Vc) and 9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-difluoropurine (VIc) were prepared from 9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-diaminopurine (IIIc). In contrast, 2,6-diamino-9-β-D-ribofuranosylpurine (IIId) gave 2-fluoroadenosine (Vd) and crotonoside (IVd) but no evidence for the formation of 2,6-difluoro-9-β-D-ribofuranosylpurine (VId) (14). It is possible, but not at all certain, that 2,6-difluoro-9-β-D-ribofuranosylpurine (VId) was formed but did not survive the isolation procedure, which was quite different from that used to isolate the nucleosides from IIIa. Since Vc, upon treatment with sodium nitrite in 48% fluoboric acid, also gave 9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-difluoropurine (VIc, 25%), it seems logical to assume that Vc is an intermediate in the conversion of IIIc to VIc. Treatment of either Vc or VIc with methanolic ammonia at 4° for three days gave an almost quantitative yield of 2-fluoroadenosine (Vd). 2′,3′,5′-Tri-*O*-acetyladenosine (VIIc) (25) was investigated next and found to give 9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl-6-fluoropurine (VIIIc) in 3.3% yield. Details are as follows. To a solution of VIIc (2.9 g., 7.35 mmoles) in 48% fluoboric acid (35 ml.) at -20° was added dropwise with stirring a solution of sodium nitrite (0.86 g., 12.5 mmoles) in water (1.8 ml.). An additional 1.2 g. (17.4 mmoles) of sodium nitrate in 25 ml. of water was added at 0° and 30 minutes later the solution was cooled to -20° and, after the addition of 90 ml. of chloroform, neutralized with 50% sodium hydroxide. The chloroform layer was removed, washed twice with water, dried over magnesium sulfate, and then evaporated to dryness. The residue was triturated with ethanol and the ethanol solution evaporated to dryness giving a semisolid residue, which was streaked on a 1 x 200 mm. SilicAR-TLC-7 coated glass plate. After the plate was developed in chloroform-methanol (19-1), the fastest traveling band was eluted, and the eluate was evaporated to dryness to give a glass which was dried over phosphorus pentoxide at room temperature and 0.05 mm.; yield, 0.1 g. (3.3%); $[\alpha]_D^{23}$ -10.8 ± 0.9° (c 0.98 g./100 ml. $CHCl_3$); λ max in mμ: ethanol – 243 (6.5), 0.1 *N* sodium hydroxide – unstable; $\bar{\nu}$ max in cm^{-1}: 3100, 2940 (CH); 1745 (C=O); 1610, 1570 (C=N, C=C); 1220, 1090, 1045, 1010 (COC). δ in ppm: 2.11, 2.14, 2.17 (C-CH_3), 4.44 m ($C_5'H$ and $C_4'H$), 5.63 t ($C_3'H$), 5.95 t ($C_2'H$), 6.25 d ($C_1'H$), 7.27 (chloroform), 8.28 (C_8H), 8.65 (C_2H). The integral of the spectrum shows 9 C-CH_3 protons, 6 sugar protons, and 2 purine protons.

Anal. Calcd. for $C_{16}H_{17}FN_4O_7 \cdot 1/5CHCl_3$: C, 46.31; H, 4.13; N, 13.33. Found: C, 46.38; H, 4.25; N, 13.27.

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