Synthesis of 9-(5-Deoxy-β-D-arabinofuranosyl)adenine[1]

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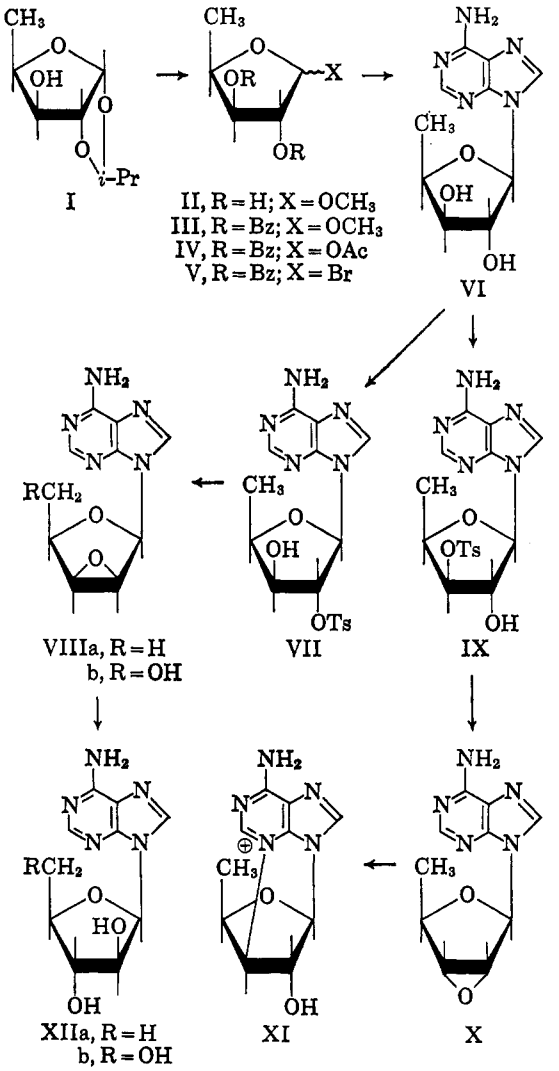
The selective monotosylation of 9-(5-deoxy-β-D-xylofuranosyl)adenine (VI) gave the 3′-O-tosylate IX from which 9-(2,3-anhydro-5-deoxy-β-D-ribofuranosyl)adenine (X) was prepared. Tosylation of the dianion of VI gave the 2′-O-tosylate VII as an intermediate which immediately cyclized to give 9-(2,3-anhydro-5-deoxy-β-D-lyxofuranosyl)adenine (VIIIa). Treatment of VIIIa with sodium benzoate in N,N-dimethylformamide (DMF) gave a mixture of 9-(5-deoxy-β-D-arabinofuranosyl)adenine (XIIa) and VI in the ratio of 2:1. The reaction of X with this same reagent appeared to involve an intramolecular epoxide opening by the adenine moiety to give a cyclonucleoside.

Spongoadenosine (9-β-D-arabinofuranosyladenine, XIIb) has shown biological activity both as a tumor inhibitor[3] and as a possible potentiating agent for other drugs.[4] Thus spongoadenosine is able to act as a nucleosidase inhibitor to prevent the enzymatic hydrolysis of thioguanosine. It competes seriously for the kinase that phosphorylates thioguanosine and converts it to a biologically active form, however; so its usefulness in this aspect is limited. It might be expected that the replacement of the 5′-hydroxyl of XIIb by hydrogen would give an analog which could not compete for this kinase but might still react satisfactorily as a nucleosidase inhibitor. For this reason, the synthesis of 5′-deoxyspongoadenosine (XIIa) was undertaken and is described in this paper.

Since the direct condensation of a 2,3-di-O-acyl-5-deoxy-D-arabinofuranosyl halide with the salt of a purine would, according to Baker's *trans* rule,[5] give predominantly the α-nucleoside, an approach similar to that used for the initial preparation of 9-β-D-arabinofuranosyl adenine[6] was investigated. The synthesis of 9-(5-deoxy-β-D-xylofuranosyl)adenine[7] (VI) was accomplished by a number of routes starting from 5-deoxy-1,2-O-isopropylidene-D-xylofuranose (I) (see Chart I).

The preparation of 9-(2,3-anhydro-5-deoxylyxofuranosyl)adenine (VIIIa) from xyloside VI requires a selective tosylation of the secondary 2′-hydroxyl of VI in the presence of the secondary 3′-hydroxyl. There are examples[8] in the literature of preferential sulfonation of a nucleoside 2′-hydroxyl in the presence of the 3′-hydroxyl, although in some cases,[8b] a mixture of 2′ and 3′ sulfonation occurs with an apparent predominance of reaction at the C-2′ hydroxyl. Examination of a molecular model of 5′-deoxyxylofuranosyladenine (VI) reveals a more favorable situation for a selective sulfonation at C-2′ than exists for the analogous riboside. The C-3′ hydroxyl is quite sterically hindered by the presence of both the adenine moiety and the C-5′ methyl group on the same side of the relatively planar sugar molecule, while the 2′-hydroxyl is alone and sterically unhindered on the opposite side of the sugar. Thus the steric availability of the 2′-hydroxyl of VI coupled with the apparent increase in reactivity of the 2′-hydroxyl over the 3′-hydroxyl toward tosylation made it reasonable to expect a considerable selectivity in the tosylation of VI to give the desired 9-[5-deoxy-2-O-(*p*-tolylsulfonyl)-β-D-xylofuranosyl]adenine (VII). Treatment of VI with 1.2 equiv. of *p*-toluenesulfonyl chloride did, indeed, give a 60% yield of a

CHART I



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(5) B. R. Baker, CIBA Foundation Symposium, The Chemistry and Biology of Purines, J. and A. Churchill, Ltd., London, 1957, pp. 120–130.

(6) (a) W. W. Lee, A. Benitez, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **82**, 2648 (1960); (b) E. J. Reist, A. Benitez, L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, **27**, 3274 (1962).

(7) The synthesis of VI by a somewhat different route has recently been reported: R. H. Shah, H. J. Schaeffer, and D. H. Murray, *J. Pharm. Sci.*, **54**, 15 (1965).

(8) (a) N. C. Yung, J. H. Burchenal, R. Fecher, R. Duschinsky, and J. J. Fox, *J. Am. Chem. Soc.*, **83**, 4060 (1961); (b) A. Todd and T. L. V. Ulbricht, *J. Chem. Soc.*, 3275 (1960).

crystalline monotosylate which was readily converted to a crystalline epoxide. When this epoxide was treated with sodium benzoate in DMF, there was considerable decomposition and the crude product isolated from the reaction appeared to have lost the adenine chromophor as shown by the disappearance of ultraviolet absorption at 260 mμ with the simultaneous appearance of absorption bands at 275 and 293 mμ. It was also observed that aqueous solutions of this epoxide decomposed on standing to give material which showed ultraviolet absorption at 293 mμ. This shift in the ultraviolet spectrum is suggestive of cyclonucleoside formation to a compound such as XI and is analogous to an observation of Baker and Joseph[9] on the intramolecular cyclization of the 5′-methylsulfonyl nucleoside of 6-dimethylaminopurine to give ultimately an imidazole derivative. For such an interaction to occur, however, it would be necessary for the epoxide to be in the *ribo* configuration (X) rather than the expected *lyxo* configuration (VIII). Such an epoxide could arise only from the 3′-O-tosylate IX. That the tosylation of VI did indeed give the 3′-O-tosylate was confirmed by n.m.r. spin-decoupling experiments which showed that the free hydroxyl was on C-2. The preferential tosylation of the 3′-hydroxyl over the 2′-hydroxyl is a very surprising result. It might possibly be rationalized on the basis of hydrogen bonding between the 3′-hydroxyl and the N-3 of the adenine which could make the 3′-hydroxyl more basic and hence more reactive than the 2′-hydroxyl even under the sterically unfavorable circumstances. If such an argument were true, it might be expected that, if hydrogen bonding could be removed such as by the preparation of the dianion of VI, the electronic advantage of the 3′-hydroxyl could be overcome and steric considerations would then control the direction of tosylation and give the desired 2′-tosylate VII. With this in mind, VI was treated with 2 moles of sodium hydride, followed by a slight molar excess of *p*-toluenesulfonyl chloride. The product from this reaction was an epoxide which proved to be the lyxoside VIIIa and hence must have arisen from the intermediate anion of the 2′-O-tosylate VII. It is interesting to note that the 3′-O-tosylate showed an extraordinary resistance to further tosylation to form the 2′,3′-ditosylate of VI.

Treatment of the anhydrolyxoside VIIIa with sodium benzoate in DMF effected the opening of the epoxide ring to give a mixture of 9-(5-deoxy-β-D-arabinofuranosyl)adenine (XIIa) and the xyloside VI in the ratio of 2:1. The arabinoside could be separated from VI by fractional crystallization from water.

The relatively large amount of xyloside VI obtained from the reaction of sodium benzoate in DMF on the 5′-deoxylyxoside VIIIa is surprising when compared with the almost exclusive formation of an arabinoside (XIIb, spongoadenosine) when this reagent was used to open 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine[6a] (VIIIb). This difference illustrates the complexities involved in ring openings of such 2,3-anhydropentofuranosides.

A study on the opening of epoxides VIIIa and X is being conducted and will be the subject of a subsequent paper.

(9) B. R. Baker and J. P. Joseph, *J. Am. Chem. Soc.*, **77**, 15 (1955).

Experimental Section[10]

1-O-Acetyl-2,3-di-O-benzoyl-5-deoxy-D-xylofuranose (IV).—A solution of 10 g. (57.5 mmoles) of 5-deoxy-1,2-O-isopropylidene-D-xylofuranose (I)[11] in 175 ml. of methanol which contained 4.0 ml. of concentrated hydrochloric acid was heated at reflux for 1 hr. The solution was cooled to room temperature, neutralized to pH 7 with IR45 (OH), then filtered, and evaporated to dryness *in vacuo*. The residue was dissolved in 50 ml. of chloroform, then filtered to remove traces of resinous material. The filtrate was evaporated to dryness *in vacuo* to give 8.1 g. (95%) of methyl 5-deoxy-D-xylofuranoside (II) as a yellow sirup. The n.m.r. spectrum of the sirup showed bands of equal intensity at τ 5.08 (d, J = 4 c.p.s.) and 5.23 (s, C-1 protons of the α and β anomers, respectively), 6.54 and 6.64 (s, methoxyl protons), and 8.68 (d, J = 5.5 c.p.s.) and 8.78 (d, J = 5 c.p.s., C-5 protons of the α and β anomers).

Treatment of the above methyl glycoside II (8.1 g., 54 mmoles) in 150 ml. of dry pyridine with 19 ml. (163 mmoles) of benzoyl chloride at room temperature for 20 hr. gave a quantitative yield of methyl 2,3-di-O-benzoyl-5-deoxy-D-xylofuranoside (III) as a sirup which showed no free hydroxyl absorption at 2.9 μ in the infrared and which was converted directly to the 1-O-acetate IV by treatment with 23 ml. of acetic anhydride and 12 ml. of sulfuric acid in 200 ml. of glacial acetic acid in the standard manner[12] to give 20 g. (95%) of the mixed anomers of 1-O-acetyl-2,3-di-O-benzoyl-5-deoxy-D-xylofuranose (IV) as a pale yellow sirup.

Crystallization of the sirupy 1-O-acetate IV from 75 ml. of ether gave 5.78 g. (27%) of crystalline product, m.p. 109.5–110.5°. The analytical sample was recrystallized from 80% aqueous ethanol: m.p. 111.5–112.0°; $[\alpha]^{21}D$ +54° (*c* 2, chloroform); λ_{max}^{Nujol} 5.7 (C=O), 7.85, 7.95 (benzoate C–O–C), and 8.10 (acetate C–O–C) μ.

Anal. Calcd. for $C_{21}H_{20}O_7$: C, 65.6; H, 5.24. Found: C, 65.8; H, 5.21.

The n.m.r. spectrum showed a singlet at τ 3.72 (C-1 proton) which suggested that the crystalline 1-O-acetate had the β configuration. This assignment was further substantiated by the optical rotation of the mother liquors from the crystallization from ether which was $[\alpha]^{21}D$ +96° (*c* 2.5%, chloroform).

9-(5-Deoxy-β-D-xylofuranosyl)adenine (VI). A. *Via* Glycosyl Bromide V.—A solution of 13.1 g. (34.1 mmoles) of 1-O-acetyl-2,3-di-O-benzoyl-5-deoxy-β-D-xylofuranose (IV) in 40 ml. of 1,2-dichloroethane was treated with 100 ml. of 30% hydrogen bromide in glacial acetic acid for 45 min. at room temperature. The solution was evaporated to dryness *in vacuo* at a temperature below 50° and three 50-ml. portions of dry xylene were added and evaporated *in vacuo* to remove the last traces of acetic acid. The residual glycosyl bromide V was dissolved in 150 ml. of dry xylene and the solution was added to a suspension of 33 g. (34.1 mmoles) of 49% chloromercuri-6-benzamidopurine on Celite in 1300 ml. of dry xylene. The reaction was heated at reflux for 2 hr. and then cooled and filtered. The filtrate was diluted with *ca.* 2500 ml. of petroleum ether (b.p. 88–89°). The precipitated blocked nucleoside was filtered, dissolved in 350 ml. of chloroform, and then washed with 300 ml. of 30% aqueous potassium iodide followed by 200 ml. of water. The organic layer was dried and evaporated to dryness *in vacuo*.

The blocked nucleoside was treated with 200 ml. of methanol saturated with ammonia (0°) at 100° for 4 hr. The cooled methanolic solution was evaporated to dryness *in vacuo*. The glassy residue crystallized when triturated with acetone and was filtered to give 2.4 g. (28%) of product, m.p. 229–231°. A second crop of product (VI) was obtained *via* precipitation and regeneration of its picrate for a total yield of 3.08 g. (36%).

(10) Melting points are corrected. Magnesium sulfate was used as the drying agent. Optical rotations were determined with a Rudolph photoelectric polarimeter. Paper chromatograms were run by the descending technique on Whatman No. 1 paper using 5% aqueous disodium phosphate (solvent A) and *n*-butyl alcohol–acetic acid–water (4:1:5) (solvent B) as the developing solvents. The spots were located by visual examination with an ultraviolet lamp. Adenine was used as the standard in all cases and was arbitrarily assigned a value of R_{ad} 1.00. The n.m.r. spectra were measured in deuteriochloroform unless otherwise noted; the chemical shifts are expressed as τ values using tetramethylsilane as the reference standard. N.m.r. peaks are described as s (singlet), d (doublet), t (triplet), and m (multiplet).

(11) K. J. Ryan, H. Arzoumanian, E. M. Acton, and L. Goodman, *J. Am. Chem. Soc.*, **86**, 2497 (1964).

(12) N. K. Richtmyer and C. S. Hudson, *ibid.*, **63**, 1727 (1941); **65**, 740 (1943).

Recrystallization from absolute ethanol gave the analytical sample, m.p. 232.0–232.5° dec., $[\alpha]^{24}D$ −66° (*c* 2, water), $\lambda_{max}^{pH\ 1}$ 257 mμ (ε 14,800), $\lambda_{max}^{pH\ 7}$ 259 mμ (ε 14,800), and $\lambda_{max}^{pH\ 13}$ 260 mμ (ε 14,800).

Anal. Calcd. for $C_{10}H_{13}N_5O_3$: C, 47.8; H, 5.21; N, 27.9. Found: C, 47.7; H, 5.27; N, 28.0.

Shah, *et al.*,[7] reported m.p. 227–228°, $[\alpha]^{20}D$ −66° (*c* 1, water), for VI.

B. *Via* Fusion of 6-Chloropurine with 1-O-Acetyl-2,3-di-O-benzoyl-5-deoxy-D-xylofuranose (IV).—A mixture of 4.0 g. (10.4 mmoles) of IV and 1.20 g. (7.76 mmoles) of 6-chloropurine was stirred *in vacuo* at 130° for 5 min., the mixture was cooled, 52 mg. of *p*-toluenesulfonic acid monohydrate was added, and the reaction was heated at 130° *in vacuo* for 35 min. more. The dark mixture was cooled and triturated with 30 ml. of chloroform to remove the insoluble, unreacted 6-chloropurine. The chloroform solution was evaporated to dryness *in vacuo* and the residue was dissolved in 35 ml. of methanol which had been saturated with ammonia at 0°. The ammoniacal solution was heated on the steam bath for 18 hr. and was evaporated to dryness *in vacuo*. The residue was partitioned between 50 ml. each of chloroform and water. The aqueous phase was extracted with two additional 50-ml. portions of chloroform and evaporated to dryness *in vacuo* to give 2.93 g. of brown oil. The product was purified *via* its picrate to give 0.50 g. (26%) of a tan powder, m.p. 212–214° dec., after trituration with 5 ml. of acetone. Recrystallization from ethanol gave material with m.p. 226.5–228° dec., identical with VI prepared by route A as shown by paper chromatography in solvents A and B and by infrared spectroscopy.

C. *Via* Condensation Using Titanium Tetrachloride.[13]—A mixture of 17.4 g. (45.2 mmoles) of 1-O-acetyl-2,3-di-O-benzoyl-5-deoxy-D-xylofuranose and 41.9 g. (56.5 mmoles) of 64% chloromercuri-6-benzamidopurine on Celite was heated at reflux in 1300 ml. of 1,2-dichloroethane and then 50 ml. of solvent was removed by distillation to dry the mixture. To the resulting suspension was added a solution of 6.2 ml. (57 mmoles) of titanium tetrachloride in 25 ml. of dry 1,2-dichloroethane and the reaction was heated at reflux for 19 hr. The reaction was cooled to room temperature and stirred with 850 ml. of saturated aqueous sodium bicarbonate for 1 hr.; then the two-phase system was filtered through a Celite pad. The organic layer was separated, washed with 200 ml. of 30% aqueous potassium iodide and 500 ml. of water, dried, and evaporated to dryness *in vacuo* to give 21.0 g. of crude blocked nucleoside as a tan-colored foam.

The blocked nucleoside was deacylated in 120 ml. of methanol containing 1.6 g. of sodium methoxide to give, after the usual work-up and purification *via* the picrate, 6.01 g. (53%) of product VI, m.p. 226.5–228.0° dec., which was identical in all respects with VI prepared by route A.

9-[5-Deoxy-3-O-(*p*-tolylsulfonyl)-β-D-xylofuranosyl]adenine (IX).—To a cold solution of 2.70 g. (10.8 mmoles) of 9-(5-deoxyxylofuranosyl)adenine (VI) in 60 ml. of dry pyridine was added 2.56 g. (13.5 mmoles) of *p*-toluenesulfonyl chloride in small portions with stirring and continued cooling. After the addition was complete, the reaction was left at room temperature for 2.5 days and the excess *p*-toluenesulfonyl chloride was decomposed by the addition of a small amount of ice. The decomposed reaction mixture was diluted with 20 ml. of water and extracted with three 50-ml. portions of chloroform. The chloroform extracts were washed with saturated aqueous sodium bicarbonate and water, dried, and evaporated to dryness *in vacuo* to give the product as a white solid. Recrystallization from 95% ethanol gave 2.6 g. (60%) of product in two crops, m.p. 210–212° dec. The analytical sample was recrystallized from absolute ethanol and had m.p. 213.5–214.0° dec., $[\alpha]^{22}D$ −35° (*c* 0.89, pyridine).

The n.m.r. spectrum in dimethyl sulfoxide-d_6 using tetramethylsilane as an external standard showed τ 3.63 (d, J = 5 c.p.s., hydroxyl), 4.18 (d, J = 3 c.p.s., C-1′ H), 5.18 (m, C-3′ H), and 5.4–5.6 (m, C-2′ and C-4′). Spin-decoupling from the bands of the multiplet assignable to C-2′ effected the collapse of the doublets to singlets at 3.63 and 4.18, assignable to hydroxyl and the C-1′ proton and thus demonstrated the presence of the free hydroxyl on C-2′.

Anal. Calcd. for $C_{17}H_{19}N_5O_5S$: C, 50.4; H, 4.72; N, 17.3; S, 7.91. Found: C, 50.3; H, 4.63; N, 17.2; S, 8.02.

9-(2,3-Anhydro-5-deoxy-β-D-ribofuranosyl)adenine (X).—A solution of 1.96 g. (4.84 mmoles) of IX and 320 mg. (5 mmoles) of sodium methoxide in 80 ml. of absolute methanol was heated at reflux for 15 min. The solution was cooled, neutralized with acetic acid, and evaporated to dryness *in vacuo*. The residue was triturated with 50 ml. of chloroform to separate the inorganic salts. The chloroform solution was treated with Norit and evaporated to dryness. The solid residue was recrystallized from absolute ethanol to give 875 mg. (78%) of product, m.p. *ca.* 190° dec. The analytical sample had m.p. *ca.* 190° dec., $[\alpha]^{26}D$ +42° (*c* 0.86, chloroform), $\lambda_{max}^{pH\ 1}$ 257 mμ (ε 14,500), $\lambda_{max}^{pH\ 7}$ 259 mμ (ε 14,400), and $\lambda_{max}^{pH\ 13}$ 259 mμ (ε 14,300).

Anal. Calcd. for $C_{10}H_{11}N_5O_2$: C, 51.5; H, 4.75; N, 30.0. Found: C, 51.7; H, 4.65; N, 30.0.

9-(2,3-Anhydro-5-deoxy-β-D-lyxofuranosyl)adenine (VIIIa).—A solution of 1.50 g. (5.98 mmoles) of VI in 35 ml. of dry DMF was cooled to −5° in an ice–salt bath and 600 mg. (14.5 mmoles) of 58% sodium hydride in mineral oil was added slowly with stirring. After the gas evolution had subsided (*ca.* 10 min.), 1.26 g. (6.63 mmoles) of *p*-toluenesulfonyl chloride was added with continued stirring and cooling. The reaction was kept at 0° for 3 days and then it was neutralized to pH 6 with glacial acetic acid and evaporated to dryness *in vacuo*. The residue was extracted with 75 ml. of hot methanol and the product was isolated from the methanol solution *via* its picrate to give 880 mg. (63%) of white solid. Crystallization from ethanol gave the analytical sample, m.p. 208–209° dec., $[\alpha]^{24}D$ −23° (*c* 2, water).

Anal. Calcd. for $C_{10}H_{11}N_5O_2$: C, 51.5; H, 4.75; N, 30.0. Found: C, 51.3; H, 4.75; N, 30.1.

9-(5-Deoxy-β-D-arabinofuranosyl)adenine (XIIa).—A solution of 200 mg. (0.86 mmoles) of VIII and 300 mg. of sodium benzoate in 20 ml. of 95% aqueous DMF was heated at 140° for 10 hr. and evaporated to dryness *in vacuo*. The residue was partitioned between chloroform and water and the water layer was evaporated to dryness *in vacuo*. The residue was purified *via* its picrate to give, after its regeneration with Dowex 2 (CO_3), 155 mg. (72%) of nucleoside mixture as a white foam which showed two spots on paper chromatography in solvent B with R_{Ad} values of 1.2 and 1.4 due to the arabinoside XIIa and xyloside VI, respectively. Crystallization from water gave the product XIIa, m.p. 163–164°. The analytical sample was obtained by recrystallization from water and had m.p. 173.5–174.5°, $[\alpha]^{21}D$ −7° (*c* 0.4, water).

Anal. Calcd. for $C_{10}H_{13}N_5O_3 \cdot H_2O$: C, 44.7; H, 5.58; N, 26.0. Found: C, 44.9; H, 5.62; N, 26.0.

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(13) J. Prokop and D. H. Murray, *J. Pharm. Sci.*, **54**, 359 (1965).