Tetraethylammonium Borodi(1-hydroxy-2-naphthoate).—A solution of 1-hydroxy-2-naphthoic acid, obtained from Matheson Coleman and Bell (18.8 g., 0.1 mole), in ethanol was shaken with charcoal and Celite and filtered. To the filtrate were added successively a solution of boric acid (3.1 g., 0.05 mole) in hot water and tetraethylammonium hydroxide (75 ml. of a 10% aqueous solution). The dark, sticky residue obtained by removal of the solvents was crystallized from ethanol–ether. Two crops of crude solid totaling 20.3 g. (79%) were obtained. Recrystallization from ethanol–ether followed by two crystallizations from 2-propanol–ether gave the analytical sample, m.p. 152–155°.

Anal. Calcd. for $C_{30}H_{32}BNO_6$: N, 2.73. Found: N, 2.70.

Tetraethylammonium Borodi(2-hydroxy-1-naphthoate).—A mixture of boric acid (6.2 g., 0.1 mole), 2-hydroxy-1-naphthoic acid (37.6 g., 0.2 mole), and tetraethylammonium hydroxide (147 ml. of a filtered 10% aqueous solution) was dissolved in a large volume of water and ethanol by boiling. Cooling and filtration gave 36.2 g. (71%) of white crystals, m.p. 179–183° after two crystallizations from ethanol.

Anal. Calcd. for $C_{30}H_{32}BNO_6$: N, 2.73. Found: N, 2.67.

An Alternative Synthesis of 2′,3′-Dideoxyadenosine[1]

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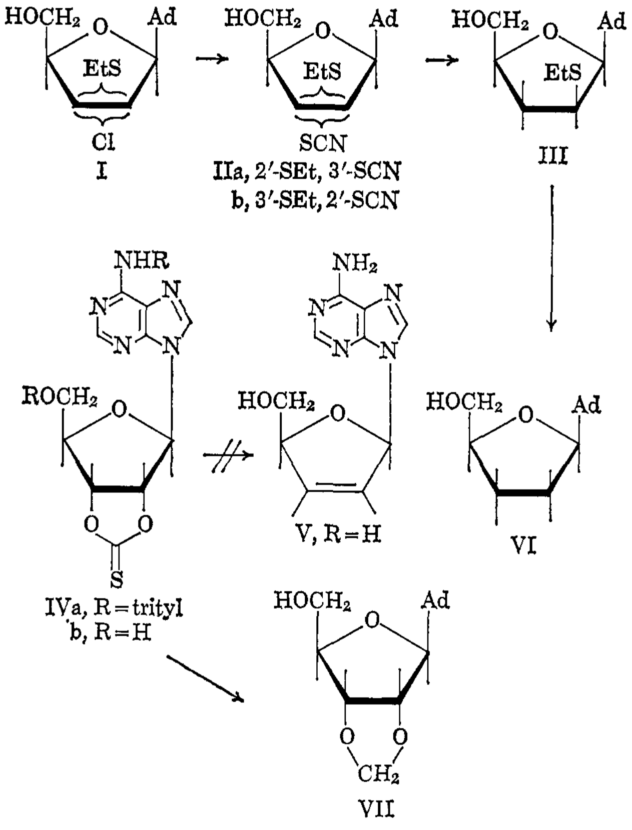
The reasons for interest in 2′,3′-dideoxyadenosine (VI) were discussed and the synthesis of VI was reported in a recent paper.[2] This report prompts us to describe our synthesis of 2′,3′-dideoxyadenosine by a different route and our attempts to prepare VI by a third route that would have been more direct (see Scheme I).

Reaction of the chloro ethylthio nucleoside I[3] with a sulfur nucleophile should give a nucleoside with 2′,3′-disulfur substitution that could undergo desulfurization to give VI. Preliminary experiments with the sodium salts of benzyl and ethyl mercaptan, potassium thiobenzoate, and potassium thiocyanate showed that only the last compound was a suitable reagent. The other compounds caused cleavage of the nucleoside to adenine. Heating the nucleoside I with potassium thiocyanate in methanol under nitrogen afforded the 3′-thiocyanate nucleoside IIa, presumably *via* an episulfonium ion intermediate,[3] as the only isolable product. Traces of the isomeric 2′-thiocyanate nucleoside IIb may have been present in the initial product, but were readily removed upon recrystallization. Desulfurization of IIa with commercial sponge-nickel[4] catalyst in N,N-dimethylformamide at 100° gave a mixture of the partially desulfurized nucleoside III and dideoxyadenosine (VI). The thiocyanate group was removed much more readily than the ethylthio group. Further desulfurization of the mixture afforded VI. The last desulfurization step was very sensitive to the quality of the sponge nickel.

SCHEME I



Ad = 9-(6-aminopurinyl)

The structure of III was assigned on the basis of n.m.r. spectroscopy experiments, using decoupling techniques. The C-1′ proton of III exhibited a doublet (τ 3.60) suggesting that it was coupled to only one proton on C-2′. A decoupling experiment confirmed this assignment and established the C-2′ proton signal at τ 6.08, an expected location if the 2′-carbon atom was bonded to a sulfur atom but not if it was bonded to only carbon and hydrogen. The structure of IIa followed from that of III. The infrared spectrum and analysis both showed that the thiocyanate group was lost in the conversion of IIa to III. The ethylthio group was not affected and must therefore be at C-2′ in IIa as well as in III. The thiocyanate group must be at C-3′.

The cyclic thionocarbonate derivatives of Corey and Winter[5] and of Horton and Turner[6] seemed promising for the conversion of adenosine (or other ribosyl nucleosides) to an olefin derivative and then to 2′,3′-dideoxyadenosine (or other dideoxy nucleosides). Using a blocked nucleoside model, it was found that N^6,5′-O-ditrityladenosine[3b] and thiocarbonyldiimidazole[7] reacted readily by Horton and Turner's procedure[6] to give the 2′,3′-O-thionocarbonato nucleoside IVa. However, all attempts to carry IVa through the rest of the projected reaction sequence to 2′,3′-dideoxyadenosine were unsuccessful. Starting without blocking groups, it was possible to convert adenosine to the 2′,3′-O-thionocarbonate IVb, but attempts to convert

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[2] M. J. Robins and R. K. Robins, *J. Am. Chem. Soc.*, **86**, 3585 (1964).

[3] (a) C. D. Anderson, L. Goodman, and B. R. Baker, *ibid.*, **80**, 6453 (1958). (b) *Ibid.*, **81**, 3967 (1959). (c) The sharp melting point of I suggested that it may be one isomer; however, n.m.r. spectroscopy suggests it is a mixture with two C-1′ doublets centered at τ 3.48 and 3.96.

[4] Product of W. R. Grace Co., 50% solids in water.

[5] E. J. Corey and R. A. E. Winter, *J. Am. Chem. Soc.*, **85**, 2677 (1963).

[6] D. Horton and W. N. Turner, *Tetrahedron Letters*, 2531 (1964).

[7] H. A. Staab and G. Walther, *Ann.*, **657**, 98 (1962).

this to the olefin V by treatment with trimethyl phosphite or deactivated sponge nickel[5] afforded only intractable oils. In one experiment with sponge nickel[4] a small amount of the crystalline 2′,3′-O-methylene nucleoside VII was isolated. A similar reductive desulfurization with Raney nickel that converted a dialkoxythionocarbonate to a dialkoxymethane has been observed by Foster and Wolfrom.[8]

Experimental[9]

6-Amino-9-[(2′,3′-dideoxy-2′-ethylthio-3′-thiocyanato)-β-D-arabinofuranosyl]purine (IIa).—A solution of 2.00 g. (6.06 mmoles) of the chloro ethylthio nucleoside I and 5.88 g. (60.6 mmoles) of potassium thiocyanate (dried at 56° and 1 mm. over phosphorus pentoxide for 20 hr.) in 200 ml. of absolute methanol was refluxed under a nitrogen atmosphere for 24 hr. After removing the solvent *in vacuo*, the residue was dissolved in 300 ml. of ethyl acetate, washed three times with 50-ml. portions of water, dried, treated with charcoal, and filtered. Evaporation *in vacuo* of the filtrate left 1.77 g. of yellowish white solid, m.p. 166.5–168° dec. (softens at 157°), which showed a main spot (R_{Ad} 1.42, solvent I) with a minor contaminant (R_{Ad} 1.27, solvent I) on paper chromatograms. Recrystallization from 40 ml. of absolute ethanol afforded 0.94 g. (44%) of II as white fibrous needles, m.p. 181–182°, homogeneous on paper chromatograms. The product from an earlier run was recrystallized again from ethanol to afford the analytical sample of IIa: m.p. 181–181.5°, $\lambda_{\max}^{\text{Nujol}}$ 4.63 (SCN) μ, $\lambda_{\max}^{\text{pH 1}}$ 258 mμ (ε 15,900), $\lambda_{\max}^{\text{EtOH}}$ 261 mμ (ε 16,200), $\lambda_{\max}^{\text{pH 13}}$ 261 mμ (ε 16,900), $[\alpha]^{24}{}_{589}$ −202° (*c* 1.00, pyridine). It moved as a single spot in solvents I and II with R_{Ad} values of 1.42 and 1.51, respectively.

Anal. Calcd. for $C_{13}H_{16}N_6O_2S_2$: C, 44.2; H, 4.57; N, 24.0; S, 18.2. Found: C, 44.4; H, 4.71; N, 24.2; S, 18.0.

6-Amino-9-(2′,3′-dideoxy-2′-ethylthio-β-D-arabinofuranosyl)-purine (III).—A mixture of 17.4 g. of sponge nickel,[4] prewashed with N,N-dimethylformamide, and 0.868 g. (2.46 mmoles) of the thiocyanato nucleoside II in 100 ml. of N,N-dimethylformamide was stirred and heated at 100° under a hydrogen atmosphere for 24 hr. The mixture was filtered hot, the catalyst was washed twice with 50 ml. of hot N,N-dimethylformamide, and the combined filtrate was evaporated *in vacuo* to dryness. A three-phase systematic extraction[10] using 100-ml. portions of ethyl acetate and water afforded 0.198 g. (27%) of III, m.p. 216–219°, from the combined ethyl acetate extracts. (The water extracts contained 0.305 g. of a mixture of III and the dideoxynucleoside VI.) Recrystallization of III from absolute ethanol gave white crystals of III: m.p. 216–219°, $\lambda_{\max}^{\text{Nujol}}$ no SCN at 4.6–4.7 μ, $\lambda_{\max}^{0.1\,N\ \text{HCl}}$ 259 mμ (ε 14,500), $\lambda_{\max}^{\text{EtOH}}$ 261 mμ (ε 15,000), $\lambda_{\max}^{0.1\,N\ \text{NaOH}}$ 261 mμ (ε 15,500), $[\alpha]^{22}{}_{589}$ −83° (*c* 0.49, pyridine). It was homogeneous in solvents I and III with R_{Ad} 1.44 and 1.40, respectively.

Anal. Calcd. for $C_{12}H_{17}N_5O_2S$: C, 48.8; H, 5.80; S, 10.9. Found: C, 48.8; H, 5.76; S, 10.4.

6-Amino-9-[2′,3′-dideoxy-β-D-glyceropentofuranosyl]purine (2′,3′-Dideoxyadenosine, VI).—The water extracts of the above experiment (preparation of III), on evaporation gave a mixture of III and VI (estimated ratio, 19:1). The mixture from two runs weighing 0.325 g. (1.1 mmoles) of III and 6.5 g. of sponge nickel was further treated as in the preparation of III for 24 hr. to afford, from the water layer, 96 mg. (37% based on 0.325 g. of III) of crystals, m.p. 177–180.5° (softens from 162°). Recrystallization from 2 ml. of absolute ethanol afforded 41 mg. of VI: m.p. 182.5–185° (softens from 172°), lit.[2] m.p. 185–186°; $\lambda_{\max}^{\text{Nujol}}$ 3.00, 3.12 (O–H, N–H), 6.00, 6.20, 6.33 (adenine), 9.32, and 9.45 (C–OH) μ; $\lambda_{\max}^{\text{pH 1}}$ 260.5 mμ (ε 13,700); $\lambda_{\max}^{\text{pH 7}}$ 260 mμ (ε 15,000); $\lambda_{\max}^{\text{pH 13}}$ 260 mμ (ε 14,900); $[\alpha]^{20}{}_{589}$ −26.8° (*c* 1.00, water), lit.[2] $[\alpha]^{25}{}_{\text{D}}$ −25.2° (*c* 1.01, water); R_{Ad} 1.22, 1.18, and 1.17 in solvents I, III, and IV, respectively.

Anal. Calcd. for $C_{10}H_{13}N_5O_2$: C, 51.1; H, 5.57; N, 29.8. Found: C, 51.0; H, 5.42; N, 29.6.

This desulfurization is very sensitive to the quality of the sponge nickel. With some older and less active nickel, this second step goes poorly.

9-(2′,3′-O-Thionocarbonato-5′-O-trityl-β-D-ribofuranosyl)-6-(tritylamino)purine (IVa).—A solution of 7.52 g. (10 mmoles) of N[6],5′-O-ditrityladenosine[3b] and 2.32 b. (13 mmoles) of thiocarbonyldiimidazole[7] in 200 ml. of dry methyl ethyl ketone was stirred and heated at reflux for 4 hr. with exclusion of moisture. After evaporating the solution to dryness, the residue was dissolved in 200 ml. of ethyl acetate. This solution was washed with three 100-ml. portions of water, dried, treated with charcoal, and evaporated *in vacuo*. The residue, a foam, was crystallized from 250 ml. of boiling isopropyl alcohol to afford 5.58 g., m.p. 150.5–153°. A second crop, m.p. 148–151°, brought the total to 7.03 g. (85%). Recrystallization of an earlier preparation from isopropyl alcohol afforded off-white IVa·0.5(*i*-PrOH): m.p. 151–152.5°; $\lambda_{\max}^{\text{Nujol}}$ 7.50 and 7.75 (C═S?) μ; $\lambda_{\max}^{\text{acetonitrile}}$ 228 mμ (ε 35,800, shoulder), 270 (22,700), 273 (22,600), and 283 (14,700, shoulder); $[\alpha]^{24}{}_{589}$ 1.1° (*c* 1.00, chloroform); R_{Ad} 0.29 in solvent V.

Anal. Calcd. for $C_{49}H_{39}N_5O_4S \cdot 0.5C_3H_8O$: C, 73.6; H, 5.26; N, 8.49; S, 3.88. Found: C, 73.5; H, 5.27; N, 8.74; S, 3.68.

A higher melting form was isolated in later preparations, m.p. 274–275°.

Anal. Found: C, 74.0; H, 4.99; N, 8.59; S, 3.72.

9-(2′,3′-O-Thionocarbonato-β-D-ribofuranosyl)adenine (IVb).—The procedure for making IVa was applied to 5.34 g. (20 mmoles) of adenosine and 3.55 g. (20.0 mmoles) of thiocarbonyldiimidazole with 200 ml. of N,N-dimethylformamide as solvent. After the reaction and the removal of the solvent, the residue was triturated with a mixture of 200 ml. of water and 1 l. of ethyl acetate, and further washed with water and ethyl acetate to afford 3.58 g. (58%) of IVb as a light brown powder, m.p. 224–226° dec. This product was essentially like the analytical sample which crystallized out of the ethyl acetate washes. Compound IVb had m.p. 234–235° dec., $\lambda_{\max}^{\text{EtOH}}$ 241 mμ (ε 18,400) and 225 mμ (ε 17,000, shoulder), and $[\alpha]^{22}{}_{589}$ −89° (*c* 0.50, pyridine). It gave streaks in all the paper solvent systems tried.

Anal. Calcd. for $C_{11}H_{11}N_5O_4S$: C, 42.7; H, 3.56; N, 22.7; S, 10.4. Found: C, 42.5; H, 3.75; N, 22.4; S, 10.4.

9-(2′,3′-O-Methylene-β-D-ribofuranosyl)adenine (VII).—A mixture of 0.887 g. (2.87 mmoles) of thionocarbonatoadenosine (IVb) and 17.8 g. of sponge nickel catalyst[4] was treated for 16 hr. as in the preparation of III. After solvent removal, the residual oil was partitioned between 60 ml. each of ethyl acetate and water. The aqueous layer was washed twice with 60-ml. portions of ethyl acetate. Evaporation of the combined ethyl acetate solutions gave 90 mg. of gum which crystallized from 1 ml. of methanol to afford 33 mg. (4.1%) of VII, m.p. 190.5–198.5°. The analytical sample was obtained by recrystallization of 19 mg. from 0.5 ml. of methanol to yield 10 mg. of VII, white crystalline powder: m.p. 201.5–205° (softens from 182°), $\lambda_{\max}^{\text{pH 1}}$ 256 mμ (ε 14,700) and 265 mμ (ε ~12,700, shoulder), $\lambda_{\max}^{\text{pH 7}}$ 259 mμ (ε 15,300), $\lambda_{\max}^{\text{pH 13}}$ 259 mμ (ε 15,200). It had R_{Ad} 1.28 in solvent VI.

Anal. Calcd. for $C_{11}H_{13}N_5O_4$: C, 47.3; H, 4.69; N, 25.1. Found: C, 47.7; H, 4.96; N, 25.2.

The use of acetone-treated sponge nickel[5] without a hydrogen atmosphere gave an intractable oil.

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[8] A. B. Foster and M. L. Wolfrom, *J. Am. Chem. Soc.*, **78**, 2493 (1956).

[9] Melting points were taken on a Fisher-Johns apparatus. Anhydrous magnesium sulfate was used as the drying agent. Paper chromatography was done by the descending technique on Whatman No. 1 paper (except with solvent V), and the spots were detected under ultraviolet light. The solvent systems were I, benzene–methanol–water (2:6:1); II, isopropyl ether–ethanol–water (16:4.5:1); III, *n*-butyl alcohol–acetic acid–water (5:2:3); IV, *n*-butyl alcohol–water, (saturated); V, solvent I run on Schleicher and Schuell No. 2496 acetylated paper; VI, isopropyl alcohol–ammonia–water (70:5:25). The n.m.r. spectra were run in deuterated dimethyl sulfoxide using a Varian HR-60 spectrometer operated at 60 Mc. Tetramethylsilane, 5% in carbon tetrachloride, was used as external reference.

[10] J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice Hall, Inc., New York, N. Y., 1950, p. 210.