faster rate being observed in several cases for the acetylene. An extension of this solvent polarity-olefin/acetylene relative reactivity relationship to the present work shows that our acetylenes were even more relatively reactive than would be expected, for the polarity of the solvent, ethanol, is substantially less than that of the aqueous sulfuric acid used by Yates. Thus, although solvent effects have been demonstrated to play an important role in determining olefin/acetylene relative reactivities, it would seem that other factors are also operative.

Experimental Section

General. Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Kinetic data were obtained on a Beckman DB spectrophotometer. Ir spectra were run on a Beckman IR-10 while nmr spectra were run on a Varian A-60 instrument.

Ferrocenylphenylacetylene (1). This compound was synthesized in 85% yield according to the method of Rausch, *et al.*,[11] mp 128–129° (lit.[11] mp 127–128°).

Iodoferrocene. Iodoferrocene, utilized in the synthesis of **1**, was initially prepared according to the method of Nesmeyanov.[12] This method, which involves the preparation of the intermediate compound chloromercuriferrocene,[13] proved to be very time consuming and gave us at best a 35% yield based upon starting ferrocene. A new method, patterned after the synthesis of halobenzenes utilizing thallic trifluoracetate (TTFA),[14] was improvised. To a solution of 3.82 g of ferrocene in 500 ml of glyme at 40° was added 5 g of TTFA in small increments over the period of 1 hr. The resulting solution was stirred at 40° for 4 hr,[15] after which time it was shaken with 250 ml of a saturated solution of aqueous potassium iodide. The organic layer was separated, dried over calcium chloride, and evaporated to yield crude iodoferrocene as a viscous, red-orange oil which was purified *via* silica gel column chromatography. The purified iodoferrocene was obtained in 88% yield, mp 50–51° (lit.[16] mp 49–49.5°). It should be stressed that subsequent attempts to prepare iodoferrocene *via* this new method have not duplicated the high yield obtained on the first run. Efforts to ascertain what was done differently on the initial trial have not met with success. However, it is suggested that freshly prepared TTFA[17] be used.

Reaction of Ferrocenylphenylacetylene (1). A 100-ml portion of a 5×10^{-2} *M* ethanolic solution of **1** was stirred at room temperature with 0.2 ml of 25% sulfuric acid. The solution was neutralized and stripped of solvent on a rotary evaporator to yield a viscous red-brown oil, which when recrystallized from benzene–hexane (75:25) gave a quantitative yield of ferrocenyl benzyl ketone (**3**), mp 129–130° (lit.[18] mp 128°). **3** was identified by comparing its melting point, ir, and nmr spectra with those of an independently prepared sample.[18]

Ethynylferrocene (6). This compound was prepared from acetylferrocene using the method of Rosenblum, *et al.*[19] An 82% yield of **6** was obtained, mp 53–54° (lit.[19] mp 51–53°).

Vinylferrocene (8). This compound was prepared in 20% yield by dehydrating α-hydroxyethylferrocene according to the method of Arimoto and Haven,[20] mp 45–47° (lit.[20] mp 48–49°).

Phenylacetylene (7). This compound was purchased from Aldrich Chemical Co. (No. 11, 770-6) and was used without further purification.

Styrene (9). This compound was purchased from Aldrich Chemical Co. (No. S497-2) and fractionally distilled prior to use.

Kinetic Data. Rates for the acid-catalyzed hydration reactions were obtained by using uv spectroscopy[21] to follow the disappearance of starting material. In each run, 3 ml of a 5×10^{-3} *M* ethanolic solution of compound was placed in the cuvette in the spectrophotometer and allowed to reach an equilibrium temperature of 31°, after which 0.1 ml of 25% H_2SO_4 was added.

Identification of Hydration Products. The hydration products listed in Table I were identified by comparing melting points and ir and nmr spectra with those of an authentic sample of the compound in question. Acetylferrocene was prepared according to the method of Broadhead, *et al.*,[22] with a 45% yield being obtained, mp 83–84° (lit.[23] mp 83–85°). α-Hydroxyethylferrocene (**12**) was prepared by $LiAlH_4$ reduction of acetylferrocene according to the method of Arimoto and Haven[20] to obtain an 80% yield, mp 70–71° (lit.[20] mp 69–72°).

Styrylferrocene (13). This compound was prepared according to the general method of Arimoto and Haven by which vinylferrocene was prepared. Ferrocene carboxaldehyde was treated with the Grignard reagent of benzyl bromide to give α-ferrocenyl-β-phenylethanol (**15**) in 80% yield, mp 80–81° (lit.[18] mp 82.3°). A 1-g portion of **15** was dissolved in a minimum amount of dry benzene to which sufficient alumina (Baker, acid washed, activity 1) was added to form a thick slurry. After standing over the alumina for 24 hr in a nitrogen atmosphere, the solution was eluted and stripped of solvent to yield crude styrylferrocene in 75% yield. After recrystallization from hexane a melting point of 123–124° was found (lit.[18] mp 120–121.5°).

Registry No.—**1**, 51108-02-2; **6**, 12764-67-9; **7**, 536-74-3; **8**, 1271-51-8; **9**, 100-42-5.

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Syntheses of Potential Antimetabolites. XV. Syntheses of a Sulfonate Analog of Adenosine 5′-Phosphate and an Alternative Synthesis of 5′,8-*S*-Anhydroadenine Nucleosides and 5′-Deoxyspongoadenosine and Its Isomers[1]

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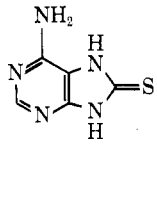
It has been well documented that *S*-anhydropurine nucleosides[2,4] as well as anhydropyrimidine nucleosides[3] are versatile intermediates for the interconversion of the nucleoside. In the preparation of 5′,8-*S*-anhydropurine nucleosides by a general procedure starting with preformed purine nucleosides, N^3,5′-cyclopurine nucleoside forma-

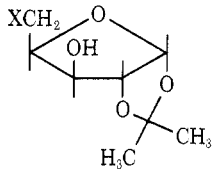
tion is quite often encountered.[5-8] In order to avert this side reaction, we developed an alternative synthetic procedure for the 5′,8-*S*-anhydroadenine nucleosides. Our new approach to the anhydro nucleoside consists in the initial synthesis of appropriate 8-alkylthioadenines, followed by the formation of an *N*-glycosyl bond. By this approach the unfavorable quaternization at N-3 could be avoided. Another and more important advantage inherent in this approach is that the anhydropurine nucleosides obtained must be the β nucleosides in the case of D-series sugars, irrespective of the kind of sugars as well as their protecting groups.[9]

In the present paper, we first deal with a novel synthetic procedure for 5′,8-*S*-anhydroadenine nucleosides (**9**, **10**, and **11**) and secondly with the conversion of these anhydro nucleosides to 9-(5-deoxy-β-D-xylofuranosyl)adenine-5′-sulfonic acid (**16**) and a number of 5′-deoxyadenine nucleosides.

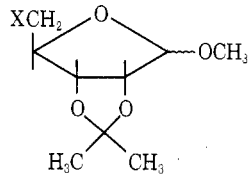
Treatment of the sodium (**1a**) or potassium salt (**1b**) of adenine-8-thione[10] with methyl 5-deoxy-5-iodo-2,3-di-*O*-acetyl-D-arabinofuranoside (**4a**) in refluxing methoxyethanol afforded a 40% yield of 8-(methyl-5-deoxy-2,3-di-*O*-acetyl-β-D-arabinofuranos-5-yl)thioadenine (**7**). The reaction of the sodium salt of adenine-8-thione (**1a**) with methyl 5-*O*-(*p*-toluenesulfonyl)-2,3-di-*O*-acetyl-D-arabinofuranoside (**4b**) gave the same result. A solution of **7** in acetic acid and acetic anhydride was treated with a small quantity of concentrated sulfuric acid at −5 to 0°. The reaction mixture was kept at room temperature for 2 days. After work-up (see Experimental Section), removal of the blocking group with methanolic ammonia gave rise to 5′,8-*S*-anhydro-β-D-arabinofuranosyladenine-8-thiol (**11**) in



1a, Na
b, K



2a, X = I
b, X = OTs



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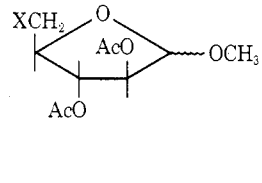

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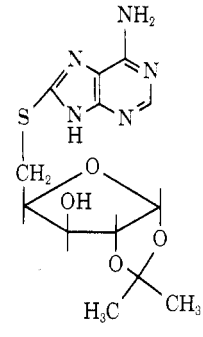

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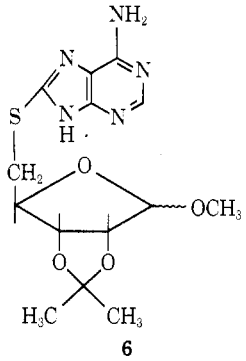

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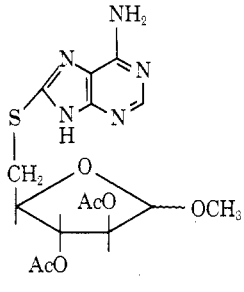

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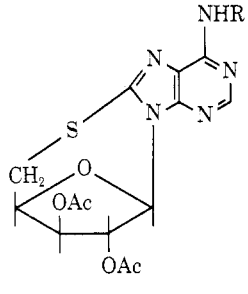
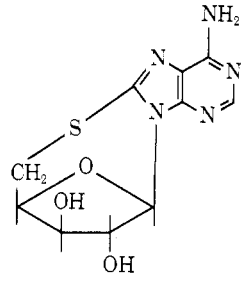


8a, X = H
b, X = CH_3CO



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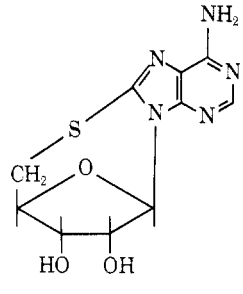

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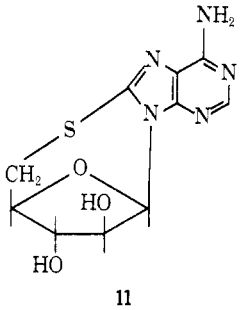

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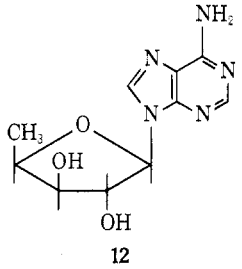

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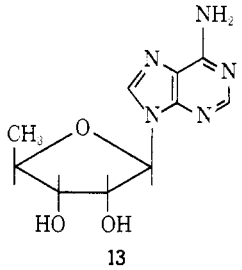

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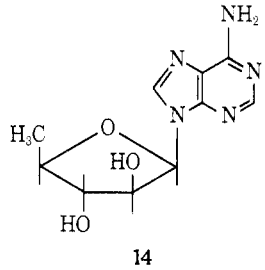

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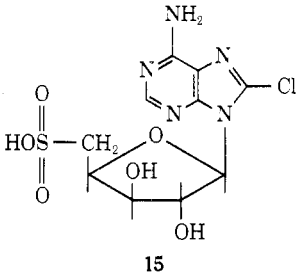

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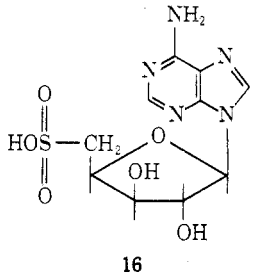

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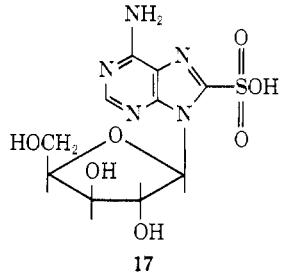

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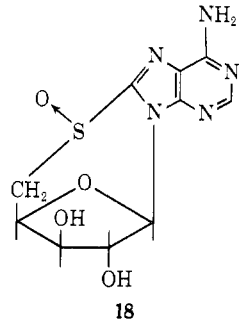

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Table I

Compd	Mp, °C	Yield, %	R_f A[a]	R_f C[a]	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
12	228–229	65	0.51	0.69	47.77	5.21	27.88	47.65	5.31	27.61
13	204	61	0.54	0.62	47.77	5.21	27.88	47.55	5.35	27.58
14	174–175	58	0.49	0.61	47.77	5.21	27.88	47.80	5.00	27.81

[a] Solvent system.

40% yield. Structural confirmation rests upon elemental analysis, spectral data, and the fact that Raney nickel treatment led **11** to 5′-deoxy-β-D-arabinofuranosyladenine (5′-deoxyspongoadenosine, **14**).[12]

The "acetic acid–acetic anhydride–sulfuric acid treatment" (at higher temperature) has been previously employed for the acetolysis of the *N*-glycosyl bond of a guanosine derivative.[11] In the present case, the reaction proceeded in reverse direction, that is, an *N*-glycosyl bond was formed.

A series of parallel reactions starting from 5-iodo-5-deoxy-1,2-isopropylidene-β-D-xylofuranoside (**2a**)[13,14] or methyl 5-iodo-5-deoxy-2,3-*O*-isopropylidene-D-ribofuranoside (**3a**)[15] gave rise to the corresponding anhydroadenine nucleosides (**9** or **10**) in overall yields of 44 and 20%, respectively. Again, 5-*O*-(*p*-toluenesulfonyl) derivatives **2b**[14] and **3b**[15] were able to replace **2a** and **3a** without reduced yields of **9** and **10**. Structural confirmation of **9** and **10** was performed on the basis of uv spectra and Raney nickel reduction. On the reduction, these two anhydro nucleosides afforded the corresponding 5′-deoxyadenine nucleosides **12**[12,17] and **13**.[18] Uv absorption maxima of these nucleosides **9**, **10**, and **11** did not shift in both acidic and basic pH regions, indicating that these compounds were 8,9 disubstituted.

The low yield with the ribose series was due to the formation of a significant amount of chloroform-insoluble and uv-absorbing by-product of unknown structure on acetic acid–acetic anhydride–sulfuric acid treatment. It is worthy of note that no indication of the presence of isomeric 7,8-disubstituted anhydro nucleosides was found in spectral and chromatographic data.

Treatment of a methanol solution of **9** with chlorine in the presence of hydrogen chloride gave rise to 5′-deoxy-β-D-xylofuranosyl-8-chloroadenine-5′-sulfonic acid (**15**) in 30% yield, which could be reduced to 9-(5-deoxyl-β-D-xylofuranosyl)adenine-5′-sulfonic acid (**16**) in quantitative yield. Oxidation of **9** with 30% hydrogen peroxide in acetic acid afforded an 81% yield of 9-β-D-xylofuranosyladenine-8-sulfonic acid (**17**). Nucleosides **16** and **17** moved as monoanions on paper electrophoresis at pH 8.5. Treatment of **9** with an aqueous solution of *N*-bromosuccinimide gave rise to the corresponding sulfoxide **18** in 71% yield, which in turn returned to the original anhydro nucleoside **9** on zinc powder reduction. Combustion values and nmr spectra of **18** were as expected for the assigned structure. The sulfoxide was a key intermediate for the conversion of a 5′,8-*S*-anhydro nucleoside to a normal nucleoside by Pummerer rearrangement.[4]

Experimental Section

Infrared (ir) spectra were determined with a Hitachi spectrometer. Ultraviolet (uv) spectra were determined using a Hitachi spectrophotometer. Nuclear magnetic resonance (nmr) spectra were determined with a high-resolution nmr spectrometer in deuteriochloroform. The chemical shifts were reported in parts per million downfield from tetramethylsilane as internal standard. Melting points were uncorrected. Before concentration the solution was dried over magnesium sulfate overnight. Solvents were removed in a rotating evaporator by a water aspirator (*ca.* 12 mm). Paper electrophoresis was performed on Toyo-Roshi paper No. 51A (10 × 40 cm) at pH 7.5 in 0.05 *M* triethylammonium bicarbonate (700 vol). Paper chromatography was performed on Toyo-Roshi paper 51A by the ascending technique. Solvent systems employed were (a) *n*-BuOH–H_2O (84:16); (b) EtOH–1 *M* AcOH (5:2); (c) *i*-PrOH–NH_4OH–H_2O (7:1:2). R_f (A) and R_f (B) in tlc (silica gel) refer to the systems $CHCl_3$–C_2H_5OH (35:5) and $CHCl_3$–C_2H_5OH (35:1), respectively. Spots were detected either by a sulfuric acid spray reagent or under the uv light.

Methyl 5-Iodo-5-deoxy-2,3-di-*O*-Acetyl-D-arabinofuranoside (4a). To a solution of methyl 5-*O*-(*p*-toluenesulfonyl)-D-arabinofuranoside (14 g, 44 mmol) in pyridine (63 ml) was added acetic anhydride (35 ml) at room temperature. The solution was allowed to stand overnight at this temperature. Water (2 ml) was then added to the solution at 0°. After 2 hr the solution was concentrated to dryness. The residue was dissolved in chloroform. The solution was washed with water, dried, and filtered. The filtrate was concentrated to dryness. Crystallization from ethanol afforded the analytical sample (**4b**, 16.5 g, 89%), mp 149–150°.

Anal. Calcd for $C_{17}H_{22}O_9S$: C, 50.75; H, 5.50; S, 7.96. Found: C, 50.55; H, 5.08; S, 7.80.

To a solution of methyl 5-*O*-(*p*-toluenesulfonyl)-2,3-di-*O*-acetyl-D-arabinofuranoside (7.65 g, 19 mmol) in acetone (50 ml) was added sodium iodide (7.6 g). The solution was heated for 6 hr at 100° (bath temperature) in a stoppered vessel. The solvent was removed to leave a gummy substance, which was dissolved in chloroform. Insoluble material was filtered off. The filtrate was washed with water, dried, and filtered. The filtrate was concentrated to dryness (5.74 g, 83%). This sample was used for the preparation of 8-alkylthioadenine (**7**).

8-(Methyl-2,3-di-*O*-acetyl-5-deoxy-D-arabinofuranos-5-yl)-thioadenine (7). Adenine-8-thione[10] was converted into the potassium salt by dissolving in methanol containing an equivalent amount of potassium hydroxide. The salt obtained by removal of solvent was used for the subsequent experiment without purification. The sodium salt **1a** was prepared similarly. The potassium salt of adenine-8-thione (2.8 g, 13.6 mmol) and **4a** (4.0 g, 10 mmol) were dissolved in methoxyethanol (40 ml). The solution was heated at reflux for 3.5 hr. The solution was concentrated to dryness. The residue was triturated with water (30 ml). Insoluble material was filtered off. The filtrate was concentrated to dryness. The residue was dissolved in methanol (10 ml). Insoluble material was again filtered off. The filtrate was concentrated to dryness. The residue was triturated with chloroform. The crude product was purified over silica gel column chromatography (silica gel, 200 g, $CHCl_3$–EtOH, 35:5). Eluate having R_f (A) 0.45 in tlc was pooled. The solvent was removed. The residue was crystallized from aqueous methanol: mp 233–235° dec; yield 12.87 g (70%); uv λ_{max} (pH 1) 287 nm, λ_{max} (pH 11) 285 nm, λ_{max} (H_2O) 285 nm.

Anal. Calcd for $C_{15}H_{19}N_5O_6S$: C, 47.59; H, 5.42; N, 19.82; S, 11.03. Found: C, 47.43; H, 5.41; N, 19.83; S, 11.12.

8-(1,2-*O*-Isopropylidene-5-deoxy-D-xylofuranos-5-yl)thioadenine (5). The sodium salt of adenine-8-thione (**1a**, 3.6 g, 19 mmol) and 1,2-*O*-isopropylidene-5-iodo-5-deoxy-D-xylofuranose (**2a**, 6.3 g, 21 mmol) was dissolved in methoxyethanol (120 ml). The solution was heated at reflux for 4 hr. The solvent was evaporated to give crude product, which was washed with water and then with acetone. Crystallization from acetone gave the analytical sample: 1.7 g (70%); mp 220–223°; uv λ_{max} (pH 1) 287 nm, λ_{max} (pH 11) 285 nm; ppc R_f (solvent system A) 0.89, R_f (solvent system B) 0.87.

Anal. Calcd for $C_{13}H_{17}N_5O_4S$: C, 46.10; H, 4.73; N, 20.69; S, 12.97. Found: C, 45.80; H, 4.54; N, 20.64; S, 12.78.

8-(Methyl-2,3-*O*-isopropylidene-5-deoxy-D-ribofuranos-5-yl)thioadenine (6). The sodium salt of adenine-8-thione (**1a**, 3.6 g, 19 mmol) and methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-D-ribofuranoside (**3a**, 5.66 g, 19 mmol) were dissolved in methoxyethanol (100 ml). The solution was refluxed for 5.5 hr. Work-up, as described above for **5**, gave the analytical sample, yield 4.96 g (74%), mp 274–275°.

Anal. Calcd for $C_{14}H_{19}N_5O_4S$: C, 47.59; H, 5.42; N, 19.82; S, 9.40. Found: C, 47.32; H, 5.64; N, 19.76; S, 9.38.

General Procedure for "Acetic Acid–Acetic Anhydride–Sulfuric Acid Treatment." Unless otherwise specified, "acetic acid–acetic anhydride–sulfuric acid treatment" was carried out as follows. To a solution of 8-alkylthioadenine (**5**, **6**, or **7**, 6 mmol) in a mixture of acetic acid (20 ml) and acetic anhydride (16 ml) was added in portions sulfuric acid (2.0 ml) at −5 to 0°. The solution was then allowed to return to ambient temperature and to stand at this temperature for 2 days. The solution was added to 650 ml of saturated sodium hydrogen carbonate solution and then completely neutralized with solid sodium hydrogen carbonate. The solution was concentrated to one-third of its volume. The solution was extracted with ethyl acetate or chloroform. The solution was washed with water, dried, and filtered. The filtrate was concentrated to dryness. The residue contained a mixture of 5′,8-*S*-anhydro-2′,3′-di-*O*-acetyl-β-D-pentofuranosyladenine and N^6,$O^{2'}$,$O^{3'}$-triacetyl-5′,8-*S*-anhydro-β-D-pentofuranosyladenine and weighed 1.0 (xylose series), 0.5 (ribose series), and 0.9 g (arabinose series), which were employed for subsequent deblocking without purification. However, isolation of two products could be achieved by silica gel chromatography (column size 3 × 30 cm, silica gel, 100 g, solvent system $CHCl_3$–EtOH 35:1).

5′,8-*S*-Anhydro-β-D-arabinofuranosyladenine-8-thiol (11). To a solution of **7** (0.8 g, 2 mmol) in acetic acid (6.6 ml) and acetic anhydride (6.0 ml) was added in drops 0.75 ml of concentrated sulfuric acid at −5 to 0°. After work-up as described above in the general procedure, crude products obtained were dissolved in methanol (24 ml) saturated with ammonia at 0°. The solution was kept at room temperature for 24 hr. The solvent was removed to leave **11**. Crystallization from aqueous methanol gave the analytical sample: yield 0.23 g (40%); uv λ_{max} (H_2O) 235 nm (ε 1.04 × 10^4), 278 (sh, 2.07 × 10^4), 285.5 (2.27 × 10^3), 295 (sh, 1.53 × 10^4); λ_{max} (0.1 *N* HCl) 277 nm (sh, 1.82 × 10^4), 285 (2.47 × 10^4), 295 (sh, 1.81 × 10^4); uv spectra in 0.1 *N* NaOH were the same as in water; R_f (solvent system A) 0.28.

5′,8-*S*-Anhydro-β-D-ribofuranosyladenine-8-thiol (10). Deblocking and recrystallization from water gave the product (0.33 g, 20%): mp 225–226°; R_f (solvent system C) 0.35; uv λ_{max} (H_2O) 237 nm (ε 8.6 × 10^3), 277 (sh, 1.78 × 10^4), 294 (sh, 1.32 × 10^4); λ_{max} (0.1 *N* HCl) 235 nm (sh, 5.2 × 10^3), 276 (sh, 1.90 × 10^4), 292 (sh, 1.58 × 10^4), 294 (sh, 1.38 × 10^4).

Anal. Calcd for $C_{10}H_{11}N_5O_3S \cdot \frac{1}{3}H_2O$: C, 41.81; H, 4.01; N, 24.39. Found: C, 41.95; H, 4.35; N, 24.18.

2′,3′-Di-*O*-Acetyl-5′,8-*S*-anhydro-β-D-xylofuranosyladenine-8-thiol (8a). Work-up and chromatography as described in the general procedure gave the product (**8a**, 1.15 g, 51%), mp 213–215° (after recrystallization from $CHCl_3$).

Anal. Calcd for $C_{14}H_{15}N_5O_5S$: C, 46.15; H, 4.15; N, 19.22; S, 8.80. Found: C, 45.98; H, 3.95; N, 19.20; S, 8.79.

5′,8-*S*-Anhydro-β-D-xylofuranosyladenine-8-thiol (9). Deblocking and recrystallization from water afforded the analytical sample: yield 0.76 g (45%); mp 267–269° dec; R_f (solvent system C) 0.38.

Anal. Calcd for $C_{10}H_{11}N_5O_3S$: C, 42.71; H, 3.94; N, 24.90; S, 11.40. Found: C, 42.61; H, 4.25; N, 24.70; S, 11.59.

Raney Nickel Reduction. A solution of 5′,8-*S*-anhydroadenine nucleosides (**9**, **10**, or **11**, 1 mmol) in 6 ml of water was refluxed with a spatulaful of Raney nickel until uv maxima did not shift. The crude solid obtained after work-up was completed was crystallized from absolute ethanol to afford a pure sample (see Table I).

9-(5′,8-*S*-Anhydro-β-D-xylofuranosyl)adenine-8-thiol *S*-Oxide (18). To a stirred suspension of **9** (281 mg, 1 mmol) in 6 ml of water was added *N*-bromosuccinimide (178 mg, 1 mmol) in 5 min. Stirring was continued until the complete solution resulted. The solution was neutralized with solid sodium hydrogen carbonate to deposit a solid substance, which was collected by filtration and washed with water: uv λ_{max} (H_2O) 262 nm; λ_{max} (pH 1) 262 nm; λ_{max} (pH 11) 265 nm; ir 1040 and 1080 cm^{-1} (^+S–O^-); yield 210 mg (71%).

Anal. Calcd for $C_{10}H_{11}N_5O_4S$: C, 40.41; H, 3.73; N, 23.56; S, 10.77. Found: C, 40.44; H, 3.77; N, 23.56; S, 10.77.

9-(5-Deoxy-β-D-xylofuranosyl)-8-chloroadenine-5′-sulfonic Acid (15). Chlorine gas was passed through a suspension of **9** (1 g, 3.57 mmol) in 50 ml of absolute methanol for 10 min at 13–18° and then hydrogen chloride gas was introduced into the suspension at this temperature for 2 hr, at which time the solution resulted. The solution was carefully concentrated to dryness below 30°. The residue was codistilled with benzene (3 × 5 ml), dissolved in 1 l. of water, and neutralized with triethylamine. The solution was applied to a DEAE-cellulose column (bicarbonate form, column size 2.5 × 35.5 cm). The column was washed with 2 l. of water (the eluate was discarded) and then washed with a linear gradient of 1 l. of water and 1 l. of 0.05 *M* triethylammonium bicarbonate, fraction size 15 ml. Fractions containing the desired product were pooled and concentrated to dryness (560 mg). An aqueous solution of the residue was treated with a IRC resin (H^+ form) and filtered. The filtrate was concentrated to dryness. The residue was crystallized from water: yield 430 mg (30%); mp 167–168° dec; uv λ_{max} (H_2O) 262.5 nm (ε 1.62 × 10^4); λ_{max} (0.1 *N* HCl) 260.5 nm (ε 1.75 × 10^4); λ_{max} (0.1 *N* NaOH) 252 nm (ε 1.64 × 10^4); ir ν_{max} (KBr) 1700 (C=NH$^-$), 1100, 1153, 1220 cm^{-1} (SO_3^-). Upon electrophoresis in 0.05 *M* triethylammonium bicarbonate (pH 8.5), the product had a mobility of 5.7 cm compared to 5.4 cm for adenosine 2′,3′-cyclic phosphate.

Anal. Calcd for $C_{10}H_{12}N_5O_6SCl \cdot HCl$: C, 29.85; H, 3.23; N, 17.41; S, 7.96; Cl, 17.66. Found: C, 30.06; H, 3.42; N, 17.20; S, 7.78; Cl, 17.66.

9-(5-Deoxy-β-D-xylofuranosyl)adenine-5′-sulfonic Acid (16). Hydrogen gas was passed through a solution of **15** (80 mg) in 20 ml of water in the presence of 10% palladium on charcoal. It required 4 hr before the hydrogen uptake ceased. The mixture was filtered. The filtrate was treated with a resin (IRC 120 OH^- form). The filtrate was concentrated to dryness. The residue was crystallized from water: yield 60 mg; mp 135° (sintering), 170–172° dec; uv λ_{max} (H_2O) 257 nm; λ_{max} (0.1 *N* NaOH) 260 nm. Upon electrophoresis in 0.05 *M* triethylammonium bicarbonate (pH 8.5), the product had a mobility of 6.4 cm compared to 6.4 cm for **15**, R_f (solvent system B) 0.04, R_f (solvent system C) 0.61.

Anal. Calcd for $C_{10}H_{13}N_5O_6S \cdot H_2O$: C, 34.38; H, 4.29; N, 20.05; S, 9.16. Found: C, 34.52; H, 4.28; N, 20.15; S, 9.20.

9-(β-D-Xylofuranosyl)adenine-8-sulfonic Acid (17). A solution of 9 (55 mg, 0.2 mmol) in 2.8 ml of acetic acid was treated with 0.4 ml of 30% hydrogen peroxide at 30° overnight, during which time crystals deposited. Recrystallization from water afforded an 81% (55 mg) yield of **17**: mp 250°; uv λ_{max} (H_2O) 262 nm (ε 1.73 × 10^4); λ_{max} (0.1 *N* NaOH) 265 nm (ε 1.70 × 10^4); λ_{max} (0.1 *N* HCl) 262 nm (ε 1.54 × 10^4); nmr 5.8 (s, 1 H, anomeric proton), 7.96 ppm (s, 1 H, H_2), absence of H_8. Upon electrophoresis at pH 8.5, the product had a mobility of 6.5 cm compared to 6.8 cm for adenosine 2′,3′-cyclic phosphate.

Anal. Calcd for $C_{10}H_{13}N_5O_7S$: C, 34.59; H, 3.77; N, 20.17. Found: C, 34.61; H, 3.88; N, 20.03.

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Registry No.—**1a**, 50600-33-4; **1b**, 50600-34-5; **2a**, 50600-39-0; **3a**, 50600-40-3; **4a**, 50600-41-4; **4b**, 50600-42-5; **5**, 50600-43-6; **6**, 50600-44-7; **7**, 50600-45-8; **8a**, 50600-46-9; **9**, 38099-23-9; **10**, 20789-80-4; **11**, 38099-25-1; **12**, 72-90-2; **13**, 4754-39-6; **14**, 4152-76-5; **15** hydrochloride, 50600-47-0; **16**, 50600-48-1; **17**, 50600-49-2; **18**, 51022-64-1; methyl 5-*O*-(*p*-toluenesulfonyl)-D-arabinofuranoside, 50600-50-5.

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Synthesis of 6-Hydroxypenicillanates and 7-Hydroxycephalosporanates

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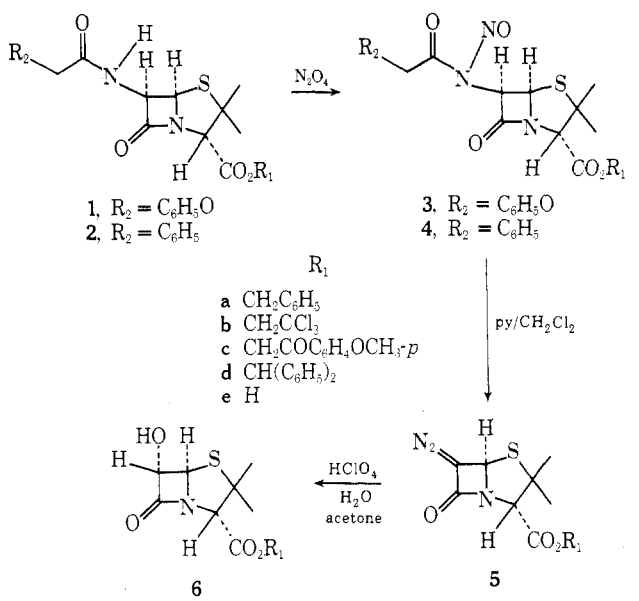
Benzyl 6-oxopenicillanate[1-3] has been shown to be a useful intermediate for the synthesis of novel β-lactam antibiotics. One precursor for this compound is benzyl 6α-hydroxypenicillanate (**6a**), derived from benzyl 6-diazopenicillanate (**5a**) (Chart I). Syntheses of **5a** have been

Chart I



reported by two methods: diazotization of 6-aminopenicillanic acid (Table I, a) or benzyl 6-aminopenicillanate (Table I, b) with nitrous acid and treatment of benzyl 6β-*N*-nitrosophenoxyacetamidopenicillanate with silica gel[4a] (Table I, c). The latter method especially suffers from a low yield. This method has been improved (Table I, c) and extended to make a greater variety of 6α-hydroxypenicillanates and 7α-hydroxycephalosporanates[4b] available.

In analogy to the diazomethane generating method with sodium hyroxide, the *N*-nitrosoamides (**3**, **4**, and **9**) should afford the diazo derivatives (**5** and **10**) on treatment with an appropriate base.

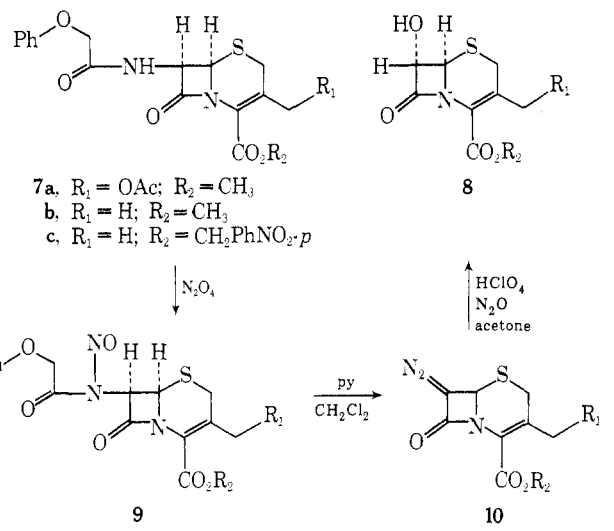
The nitrosoamides were prepared from penicillin (**1**, **2**) or cephalosporin (**7**, Chart II) derivatives according to the method of Hauser and Sigg[4a] using methylene chloride as solvent. The nitrosoamides were then treated with a base. Pyridine was found to be a better base than triethylamine for this reaction. Solvents such as ethyl acetate, methyl sulfoxide, tetrahydrofuran, and methylene chloride can be used. Refluxing methylene chloride was found to be the best solvent, resulting in the shortest reaction time and easiest removal at the end of the reaction. Table I gives the transformations to which this method has been applied and the yields. In most cases compounds **5** and **10** were hydrolyzed with perchloric acid in aqueous acetone without previous isolation.

Table I

Reaction	Yield, %
a 6-APA → **6a**	22[c]
b Benzyl 6-APA → **5a**	2.1[c]
c **1a** → **5a**	7.5[c]
d **1a** → **6a**	46
e **1b** → **6b**	30
f **1c** → **6c**	35
g **2b** → **5b**	72
h **5b** → **6b**	60
i **2b** → **6b**[a]	25
j **2e** → **6d**	7
k **7a** → **8a**	12
l **7b** → **8b**	15
m **7c** → **8c**[b]	24

[a] Without purification of **5b**. [b] Yield adjusted to account for recovered starting materials. [c] Reference 4a.

Chart II



After refluxing **4b** in methylene chloride with pyridine, a brown oil was obtained which solidified and could be recrystallized from carbon tetrachloride–petroleum ether to give β,β,β-trichloroethyl 6-diazopenicillanate (**5b**) as yellow crystals. This is the first reported isolation of an ester of 6-diazopenicillanic acid in crystalline form.[5] Pure **5b** was hydrolyzed in aqueous acetone with perchloric acid to give a 60% yield of **6b**, which was isolated by crystallization (Table I, h). Crude **5b** was hydrolyzed to give, after chromatography, **6b** in only 40% yield. Thus, working with a pure diazo compound not only resulted in a higher yield but also facilitated isolation of the product.

The *N*-nitrosocephalosporanates were found to be surprisingly resistant to rearrangement. Under the rearrangement conditions used for penicillin derivatives, 53% of the *N*-nitrosocephalosporanate **9c** was recovered. Increased reaction time or temperature resulted in loss of the β-lactam. This difference in reactivity of the nitroso derivatives **3** or **4** and **9** may be due to the steric effect of the *gem*-dimethyl group of penicillin.[6]

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were