diastereomer of (Nmen)(C_6H_5)$PCH_2CH_2P(C_6H_5)_2$ (I). Since the results were not substantially different from those obtained with the more convenient catalysts prepared in situ by reaction of $[(nor\text{-}C_7H_8)RhCl]_2$ with the phosphine (Table II), similar pure cationic salts of the other phosphines used in this work were not tested as catalysts.

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Registry No. I isomer 1, 70912-44-6; I isomer 2, 70912-45-7; II, 70912-46-8; (–)-menthol, 2216-51-5; (–)-menthyl chloride, 16052-42-9; (+)-neomenthyl chloride, 13371-12-5; phenylphosphine, 638-21-1; diphenylvinylphosphine, 2155-96-6; dimethylvinylphosphine sulfide, 42495-78-3; neomenthyldiphenylphosphine, 43077-29-8; phenyldichlorophosphine, 644-97-3; vinyl bromide, 593-60-2; sodium phenylphosphide, 51918-31-1; bis[2-(neomenthylphenylphosphino)ethyl]phenylphosphine, 70912-47-9; (Nmen)(C_6H_5)$PCH_2CH_2P(S)(CH_3)_2$ isomer 1, 70912-48-0; (Nmen)(C_6H_5)$PCH_2CH_2P(S)(CH_3)_2$ isomer 2, 70912-49-1; menthylphenylphosphine, 70912-50-4; [(Nmen)(C_6H_5)$PCH_2CH_2P(C_6H_5)_2Rh(nor\text{-}C_7H_8)$][$ClO_4$], 70940-72-6; $[(nor\text{-}C_7H_8)RhCl]_2$, 12257-42-0; menthyldiphenylphosphine, 43077-31-2; (*Z*)-2-(acetylamino)-3-phenylpropenoic acid, 55065-02-6; methyl (*Z*)-2-(acetylamino)-3-phenylpropenoate, 60676-51-9; (*Z*)-2-(benzoylamino)-3-phenylpropenoic acid, 26348-47-0; ethyl (*Z*)-2-(benzoylamino)-3-phenylpropenoate, 26348-46-9; *N*-acetyl-D-phenylalanine, 10172-89-1; *N*-acetyl-L-phenylalanine, 2018-61-3; methyl *N*-acetyl-D-phenylalaninate, 21156-62-7; methyl *N*-acetyl-L-phenylalaninate, 3618-96-0; *N*-benzoyl-D-phenylalanine, 37002-52-1; *N*-benzoyl-L-phenylalanine, 2566-22-5; ethyl *N*-benzoyl-D-phenylalaninate, 64896-35-1; ethyl *N*-benzoyl-L-phenylalaninate, 7200-18-2; phenyldivinylphosphine, 26681-88-9.

Convenient Preparation of 5′-Chloro-2′,5′-dideoxyadenosine

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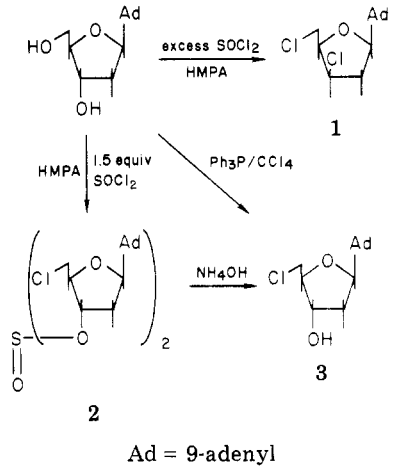
The title compound was prepared by treating 2′-deoxyadenosine with 1.5 equiv of $SOCl_2$ in hexamethylphosphoramide. An intermediate bis sulfite was isolated and characterized.

The chlorination procedure developed by Kikugawa and Inchino,[1] using hexamethylphosphoramide (HMPA) and $SOCl_2$, has been widely and successfully applied to the preparation of 5′-chloro derivatives of purine and pyrimidine ribonucleosides.[2-5] Attempts to employ this procedure in the preparation of the corresponding derivative (**3**) of 2′-deoxyadenosine, however, have in general given only the dichlorinated product, **1**.[2-4] In a single instance where selective chlorination at the 5′-position was reported,[5] **3** served as an intermediate and was not characterized.

The procedures which gave dichlorination used a considerable excess of $SOCl_2$. Our studies have revealed that reducing the amount of $SOCl_2$ to 1.5–1.8 equiv brought about a different reaction; the major product obtained, after removal of HMPA and adjustment of pH to neutrality, was the bis sulfite **2** (Scheme I), which was readily isolated and characterized by its elemental composition and NMR spectra. A similar product has been reported from the attempted chlorination of 1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)uracil, but in that case $SOCl_2$ was used in the absence of HMPA.[6]

The bis sulfite **2** was readily converted to the desired 5′-chloro derivative **3** upon standing overnight in a mixture of CH_3OH and concentrated NH_4OH. The reaction appears to proceed by sulfur–oxygen scission, since the product obtained was identical chromatographically and in its NMR spectrum with **3** prepared by chlorination of 2′-deoxyadenosine with triphenylphosphine and CCl_4.[7]

Scheme I



Ad = 9-adenyl

The latter method is unambiguous, but has the disadvantages of lower yield and higher cost, and is not well suited to larger scale preparations.

If **2** was dissolved in HMPA and treated with excess $SOCl_2$, conversion to the dichlorinated product (**1**) was rapid. This indicates that **2** may serve as an intermediate in the previously reported dichlorinations, although alternative mechanisms may be more important.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were performed by Integral Microanalytical Laboratories, Inc., Raleigh, N.C. Thin-layer chromatograms (TLC) were run on Eastman silica gel plates with a UV indicator and developed with $CHCl_3$–CH_3OH (9:1). High-pressure liquid chromatograms (LC) were run on a Whatman ODS silica gel column using mixtures of CH_3OH and H_2O at a pressure of 1700 psi; compounds were

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detected by their UV absorbance at 254 nm using an ISCO UA-5 monitor. A Varian XL-100 and a Varian CFT-20 spectrometer provided the proton magnetic resonance spectra (^{1}H NMR); chemical shifts are reported in parts per million downfield from tetramethylsilane as internal standard. UV spectra were recorded with a Varian Super Scan 3 spectrometer. XAD-2 resin (Rohm and Haas) was washed with acetone, CH_3OH, and H_2O before use. HMPA was stored over 4A molecular sieves; $SOCl_2$ was used as received from Aldrich; 2′-deoxyadenosine (Calbiochem) was dried at 70 °C in a vacuum oven overnight to remove 1 mol of H_2O, when anhydrous material was required.

9-(3,5-Dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)adenine (1). Addition of 2′-deoxyadenosine monohydrate (3.82 g, 14.2 mmol) to a stirred solution of $SOCl_2$ (6.2 mL, 86 mmol) in 40 mL of HMPA produced a red solution and generated a moderate amount of heat, which was readily controlled with an ice bath (on other occasions the addition was made to an already-chilled solution; no effect was observed on yield or product). The reaction mixture was stirred at room temperature overnight and poured onto 200 mL of ice. The resulting turbid suspension was made strongly basic with NH_4OH; this produced a clear yellow solution which was decanted from a small amount of black residue. Upon standing for several hours at 0 °C, the solution deposited a tan solid which was collected and dried, giving 2.2 g (57%) of 1. The filtrate was shown by LC to be a roughly equimolar mixture of adenine and 1. The crude product was dissolved in 1 N HCl, treated with charcoal, and precipitated by addition of 1 N NaOH to a pH of 7.5. This gave 2.17 g of white powder, pure by TLC and LC. As previously reported,[2] melting point varied with rate of heating: at 2 °C/min, mp 161–162 °C dec; UV λ_{max} (pH 1) 257 nm (ε 16 000); UV λ_{max} (pH 13) 259 nm (ε 18 500); ^{1}H NMR (80 MHz) (Me_2SO-d_6) 3.2 (m, 2, $C_{2'}$H), 3.92 (d, 2, $C_{5'}$H), 4.45 (m, 1, $C_{4'}$H), 4.90 (m, 1, $C_{3'}$H), 6.35 (dd, 1, $C_{1'}$H), 7.29 (s, 2, NH_2), 8.13 (s, 1, C_2H or C_8H), 8.24 (s, 1, C_2H or C_8H). Anal. Calcd for $C_{10}H_{11}N_5Cl_2O$: C, 41.68; H, 3.84; N, 24.30; Cl, 24.61. Found: C, 41.46; H, 3.62; N, 24.27; Cl, 24.49.

Bis(3′-*O*-5′-chloro-2′,5′-dideoxyadenosine) Sulfoxide (2). Addition of anhydrous 2′-deoxyadenosine (3.0 g, 11.9 mmol) to a stirred solution of $SOCl_2$ (1.5 mL, 21 mmol) in 30 mL of HMPA produced a clear red solution. This was stirred overnight at room temperature and diluted with 150 mL of ice water, and the resulting solution was extracted four times with 200-mL portions of $CHCl_3$. Adjustment of the pH of the aqueous phase to 7 with NH_4OH produced an immediate precipitate, which was cooled to 0 °C and collected to give 2.18 g (62%) of **2**. The product was further purified by re-precipitation from 1 N HCl by addition of 1 N NaOH. The resulting white solid gave a single peak on LC with a retention time more than twice that of **1**: mp 172–176 °C dec; UVλ_{max} (pH 1) 257 nm (ε 27 000), UV λ_{max} (pH 13) 260 nm (ε 26 000); ^{1}H NMR (80 MHz) (Me_2SO-d_6) δ 2.75–3.25 (m, 2, $C_{2'}$H), 3.90 (m, 2, $C_{5'}$H), 4.30 (m, 1, $C_{4'}$H), 5.40 (m, 1, $C_{3'}$H), 6.35 (t, 1, $C_{1'}$H), 7.25 (s, 2, NH_2), 8.05 (s, 1, C_2H or C_8H), 8.25 (s, 1, C_2H or C_8H). Anal. Calcd for $C_{20}H_{22}N_{10}Cl_2O_5S$·1.5$H_2O$: C, 39.22; H, 4.11; N, 22.86; Cl, 11.58; S, 5.24. Found: C, 38.90; H, 3.91; N, 22.89; Cl, 12.23; S, 5.35 (Karl Fisher water determination confirms sesquihydrate).

5′-Chloro-2′,5′-dideoxyadenosine (3). Method 1. A suspension of unpurified **2**, prepared as above from 12.0 g (47.6 mmol) of anhydrous 2′-deoxyadenosine, was stirred overnight in 200 mL of CH_3OH and 45 mL of concentrated NH_4OH at room temperature. The resulting clear solution was concentrated in vacuo and the residue was recrystallized from 50 mL of H_2O to give 9.0 g (68% overall) of **3** as white crystals. Product was a single spot on TLC, lower than 1: mp 120 °C softens, 162–168 °C dec; $[M]_D^{20}$ −60.5° (*c* 1.02, DMF); UV λ_{max} (pH 1) 257 nm (ε 14 600); UV λ_{max} (pH 13) 260 nm (ε 15 200); ^{1}H NMR (100 MHz) (Me_2SO-d_6) δ 2.4 (m, 1, $C_{2'\alpha}$H), 2.95 (m, 1, $C_{2'\beta}$H), 3.9 (m, 2, $C_{5'}$H), 4.05 (m, 1, $C_{4'}$H), 4.52 (m, 1, $C_{3'}$H), 5.54 (d, 1, $C_{3'}$OH), 6.45 (t, 1, $C_{1'}$H), 7.28 (s, 2, NH_2), 8.16 (s, 1, C_2H or C_8H), 8.33 (s, 1, C_2H or C_8H). Anal. Calcd for $C_{10}H_{12}N_5ClO_2$·0.5H_2O; C, 43.09; H, 4.70; N, 25.13; Cl, 12.72. Found: C, 43.20; H, 4.48; N, 25.19; Cl, 12.92.

Method 2. Addition of 1.0 mL (10 mmol) of CCl_4 to a solution of anhydrous 2′-deoxyadenosine (0.54 g, 2.2 mmol) and triphenylphosphine (1.05 g, 4.0 mmol) in 5 mL of HMPA produced a white precipitate after 45 min of stirring. Reaction was continued overnight and terminated by addition of 5 mL of CH_3OH. The resulting clear solution was poured into 200 mL of ether at 0 °C. A white precipitate formed, which was collected, washed well with ether, and dissolved in a small volume of H_2O and the pH adjusted to 7 with 1 N NaOH, producing a small amount of gummy precipitate (several spots by TLC, including 1). The supernatant was chromatographed on a 2.5 × 20 cm column of XAD-2 resin. Elution with H_2O removed salts, 10% ethanol eluted a small amount of 2′-deoxyadenosine, and 30% ethanol (300 mL) eluted **3**, which was isolated by concentrating the eluent to dryness, followed by precipitation from ethanol with ether: yield 0.20 g (32%), identical with the previous preparation by LC (0.1% 2′-deoxyadenosine present) and ^{1}H NMR; mp 137 °C softens, 169–171 °C dec; $[M]_D^{20}$ 64.2° (*c* 1.02, DMF); UV λ_{max} (pH 1) 257 nm; UV λ_{max} (pH 11) 260 nm. Anal. Calcd for $C_{10}H_{12}N_5ClO_2$·0.5EtOH: C, 45.13; H, 5.17; N, 23.92; Cl, 12.11. Found: C, 45.32; H, 4.93; N, 23.97; Cl, 11.61 [ethanolate not removed by drying at 50 °C (0.2 mm)].

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Registry No. 1, 63162-55-0; 2, 71001-16-6; 3, 57274-14-3; 2-deoxyadenosine, 958-09-8.

Practical Synthesis of Cyclic Peptides, with an Example of Dependence of Cyclization Yield upon Linear Sequence

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A convenient general procedure for the synthesis of cyclic peptides is reported. The linear intermediates, obtained via solid-phase synthesis, are cyclized by the coupling agent diphenylphosphoryl azide (DPPA). A simple procedure allows rapid isolation of the cyclic products. Peptides of varying ring size have been prepared in amounts of up to 50 g. A significant variation of cyclization yield with sequence has been observed in the conversion of three different linear peptides to the same cyclic product. Several related linear sequences have also been cyclized, and the results are discussed.

Naturally occurring and synthetic cyclic peptides have been subject to intensive study in recent years.[1] Their unique role in the binding and transport of cations and the diversity of their biological effects make them of in-

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