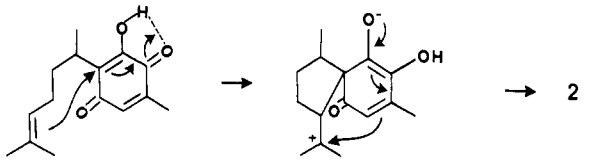
Scheme I

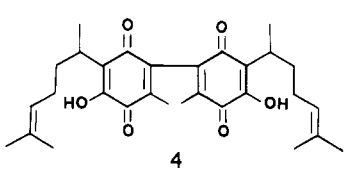


then shown[9] to be a concerted $[_\pi 4_s + _\pi 2_s]$ cycloaddition.[10] It was also noted that there is a lack of stereochemical induction by the already present chiral center of perezone (**1a**), since both α- (**2**) and β-pipitzol (**3**) are obtained in equal molar amounts, the best yield for the transformation being 70% after reflux in cumene for 20 h.

During the mechanistic study[7] of the thermolysis, an alternate[4d] stepwise path (Scheme I) was eliminated. However, if one could induce the transformation of perezone (**1a**) under mild reaction conditions by the latter mechanism, a highly stereoselective reaction should occur, since the attack of the π electrons of the double bond from the side chain is α to a chiral center. To favor such a Michael-type addition, it is necessary to polarize the quinonoid carbonyl group that is vicinal to the enol of perezone (**1**) with a suitable Lewis acid that does not contain metal atoms in order to avoid the formation of stable chelates.

When perezone (**1a**) is treated at 0 °C with 8 equiv of boron trifluoride during 30 min, it is transformed, through a highly stereoselective process, into a mixture containing 90% α-pipitzol (**2**) and 10% β-pipitzol (**3**), in 98% overall yield of isolated material. The isomerization follows the stepwise reaction mechanism since when perezone (**1b**) is used, regioselectively[11] deuterated at one of the isopropylidene methyl groups, one obtains α-pipitzol (**2**) in which the deuterium is scrambled over the two methyl groups of the *gem*-dimethyl, as was clearly seen in the 90-MHz ^{1}H NMR spectrum. The spectrum was identical with that of unlabeled pipitzols, except for the two singlets at 1.03 and 1.08 ppm, which showed the expected deuterium incorporation.

When the reaction is performed in the presence of only 0.1 equiv of BF_3, 29% of the pipitzols and 30% diperezone (**4**) were obtained. As the amount of BF_3 is increased, the



4

yield of the pipitzols increases, the pertinent data being in the experimental section. The dimer was identical, by TLC and comparison of ^{1}H and ^{13}C NMR spectra, with a sample of **4** that we have isolated very recently from the roots of *Perezia alamani* var *oolepis*.

The change in stereoselectivity for the cyclization maybe attributed to asymmetric induction at a lower reaction temperature in a process leading to a relatively stable intermediate. Since the predominant reaction product, α-pipitzol (**2**), has the same chirality as many naturally occurring cedranolides,[12] this transformation may open new avenues for biomimetic syntheses of natural products, some of them already being inspired[13] by the perezone–pipitzol transformation.

Table I

BF_3:1[a]	% pipitzols	% diperezone
0.1	29	30
0.4	32	27
0.8	37	20
1.2	65	13
4.0	76	9
8.0	98	-

[a] Molar ratio.

Experimental Section

^{1}H NMR spectra were measured with a Varian Associates EM-390 spectrometer at 90 MHz in $CDCl_3$ solutions containing tetramethylsilane as internal standard. Similar solutions were used to determine ^{13}C NMR spectra with a Varian Associates XL-100A-FT-16K system. Optical rotations, measured by using a Perkin-Elmer 141 M polarimeter, were performed at room temperature at 589 nm. Thin-layer chromatography was carried out with SiO_2 GF-254 (Merck).

Reactions of Perezone (1) with BF_3. Solutions containing 149 mg (0.6 mmol) of perezone (**1**) in anhydrous dichloromethane (10 mL) were cooled to 0 °C and treated with variable amounts (see Table I) of freshly distilled boron trifluoride etherate in dichloromethane (1 mL). After 30 min, the reaction mixtures were poured into ice–water and extracted with AcOEt. The organic layers were washed with diluted $NaHCO_3$ solutions and water, dried ($MgSO_4$), and evaporated under vacuum. The residues were separated by preparative thin-layer chromatography (SiO_2), using a mixture of hexane–benzene–chloroform–methanol (20:20:1:1). The yields of isolated products are given in Table I.

The isolated pipitzol mixture [R_f 0.53; $[\alpha]_D$ +174° (dioxane) (lit.[5] **2**, $[\alpha]_D$ +192°; **3**, $[\alpha]_D$ −172°)] was identical in all respects with an authentic mixture containing 90% **2** and 10% **3**.

Diperezone (**4**) showed R_f 0.41 and its identity was established by ^{1}H and ^{13}C NMR spectral comparison with an authentic sample.

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Registry No. **1a**, 3600-95-1; **2**, 2211-20-3; **3**, 2211-21-4; **4**, 77416-47-8; BF_3, 7637-07-2.

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New Procedure for the Chlorination of Pyrimidine and Purine Nucleosides[1]

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The 5-halo-substituted pyrimidine nucleosides and 8-halo-substituted purine nucleosides have been shown to exhibit interesting chemotherapeutic, biochemical, and

(1) A preliminary account of this work has been presented: E. K. Ryu and M. MacCoss, Abstracts, 179th National Meeting of the American Chemical Society, Houston, TX, Mar 23–28, 1980, ORGN 011.

0022-3263/81/1946-2819$01.25/0

Table I. Physical Data for Chlorinated Nucleosides

compd	NMR data[a]	UV,[b] nm (ε)	anal.[c]	mp, °C
2a	8.50 (s, H6), 5.72 (d, H1′, J = 4.4 Hz), 4.0 (m, H2′, H3′), 3.86 (m, H4′), 3.63 (m, H5′, H5″)	as previously reported[12]	$C_9H_{11}N_2O_6Cl$ (C, H, N, Cl)	220–223
2b[d]	7.85 (s, H6), 5.98 (d, H1′, J = 3.9 Hz), 3.97 (m, H2′), 3.89 (m, H3′), 3.75 (m, H4′), 3.59 (m, H5′, H5″)	(i) 299 (10 700), (ii) 287 (7900)	$C_9H_{12}N_3O_5Cl$ (C, H, N, Cl)	203–205
2c	8.17 (s, H6), 6.07 (t, H1′, J = 6.4 Hz), 4.20 (m, H3′), 3.77 (m, H4′), 3.57 (m, H5′, H5″); 2.00–2.14 (m, H2′, H2″)	(i) 297.5 (8000), (ii) 286.2 (5500)	$C_9H_{12}N_3O_4Cl$ (C, H, N, Cl)	165–167
2d[d]	8.33 (s, H6), 5.75 (d, H1′, J = 3.0 Hz), 3.98 (m, H2′, H3′), 3.89 (m, H4′), 3.73 (m, H5′, H5″)	as previously reported[13]	$C_9H_{12}N_3O_5Cl$ (C, H, N, Cl)	218–223 dec
4a	8.16 (s, H2), 5.84 (d, H1′, J = 7.0 Hz), 5.03 ("t", H2″), 4.18 (m, H3′), 3.97 (m, H4′), 3.66 (m, H5′, H5″), 7.61 (br s, NH_2)	as previously reported[15]	$C_{10}H_{12}N_5O_4Cl$ (C, H, N, Cl)	188–190
4b	8.08 (s, H2), 6.25 (d, H1′, J = 6.0 Hz), 4.33 (m, H2′, H3′), 3.73 (br s, H3′ H4′, H5′, H5″), 7.46 (br s, NH_2)	(i) 261 (16 200), (iii) 263 (15 700)	$C_{10}H_{12}N_5O_4Cl \cdot HCl \cdot 0.5H_2O$ (C, H, N, Cl)	151–153 dec
4c	5.73 (d, H1′, J = 6.4 Hz), 4.95 (m, H2′), 4.16 (m, H3′), 3.89 (m, H4′), 3.59 (m, H5′, H5″), 6.61 (br s, NH_2)	(i) 259 (15 500), (ii) 268 (13 500)	$C_{10}H_{12}N_5O_5Cl$ (C, H, N, Cl)	>260
5	7.98 (s, H2), 6.47 (d, H1′, J = 5.0 Hz), 4.41 (d, H2′, J = 5.0 Hz), 4.03 (m, H3′, H4′), 3.16 (m, H5′, H5″), 6.84 (br s, NH_2)	as previously reported[28]	$C_{10}H_{11}N_5O_4$ (C, H, N)	<190 dec

[a] Samples in Me_2SO-d_6, values in δ (from internal Me_4Si). [b] (i) 0.1 M HCl; (ii) 0.1 M NaOH; (iii) H_2O. [c] Analyses in parentheses within ±0.4 of calculated values. [d] NMR data in Me_2SO-d_6 + D_2O.

biophysical properties.[2] In addition, they have served as useful synthetic intermediates for the preparation of related nucleosides of biological interest.[3,4] The direct bromination of uracil derivatives (at C5) has been achieved previously by using Br_2–acetic anhydride,[5] Br_2–dimethylformamide (DMF),[6] Br_2–H_2O,[7] or *N*-bromosuccinimide;[8] cytosine derivatives have been brominated by using Br_2–H_2O in the presence of UV irradiation[9] or with Br_2–pyridine–acetic acid in the absence of UV.[10] Direct bromination of purine derivatives at C8 is readily achieved by using Br_2–H_2O[4] or Br_2 in sodium acetate buffer.[11] The chlorination of pyrimidine and purine derivatives has been somewhat less extensively studied, and previous methods for chlorination of pyrimidine nucleosides at C5 have included the use of Cl_2–H_2O in the presence of UV irradiation[12] and of *N*-chlorosuccinimide–acetic acid.[13] In contrast to the ease of bromination at C8 of purine derivatives,[4,11] greater difficulty has been noted with regard to chlorination. Attempts at direct chlorination, analogous to bromination, have been unsuccessful. However, the direct preparation of 8-chloroadenosine and its mono- and diphosphate derivatives has been achieved by using tetrabutylammonium iodotetrachloride[14] and by the use of *tert*-butyl hypochlorite,[15] although the yields are low.

Results and Discussion

Recent investigations in this laboratory were directed toward an examination of the N-oxidation of purine[16] and pyrimidine derivatives. In the course of this work, we examined the reaction between 1-β-D-arabinofuranosylcytosine hydrochloride (araC·HCl) and a slight molar excess of *m*-chloroperbenzoic acid (MCPBA) in an aprotic solvent such as dimethylformamide (DMF), dimethylacetamide (DMA), or hexamethylphosphorus triamide. Chromatographic evaluation (TLC) of the reaction mixture showed two major components, unreacted starting material, and a reaction product having a slightly greater R_f value. This material was subsequently identified as 1-β-D-arabinofuranosyl-5-chlorocytosine (**2d**). Of particular importance was the observation that *no* 1-β-D-arabinofuranosylcytosine N^3-oxide could be detected—in direct

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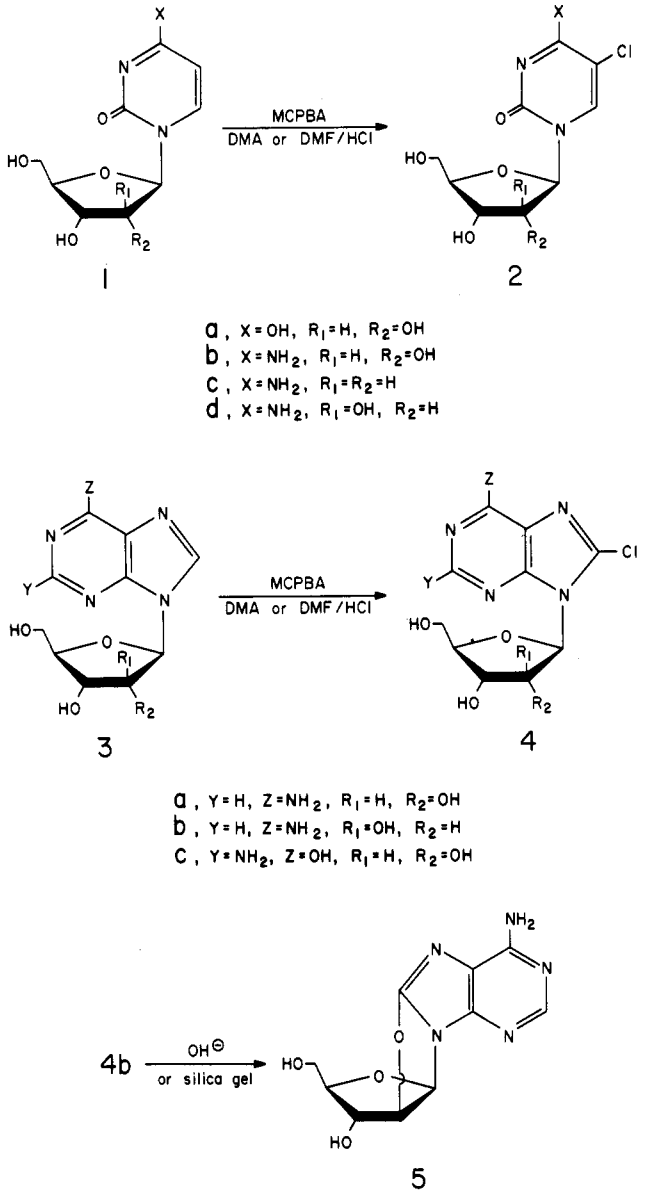
(17) The predominant tautomer of OH-substituted heterocycles (e.g., **1a**, **2a**, **3c**, and **4c**) is the keto form. The enol form is shown in the structures in Scheme I for ease of representation.

Scheme I[17]



contrast to when the free base of araC is used, since in this instance the N^3-oxide is the major product.

Following on these initial observations, we have systematically reinvestigated the reaction between MCPBA and other pyrimidine and purine derivatives in dipolar aprotic solvents containing HCl (see Scheme I and Table I). In the pyrimidine series, both uracil (**1a**) and cytosine (**1b–d**) derivatives gave the corresponding 5-chloro derivatives in high yield after a facile workup. The reaction progressed irrespective of the nature of the sugar moiety, as is demonstrated by the use of ribose, deoxyribose, and arabino sugars in the cytosine series (**1b–d**). The products were all identified by elemental analysis and by comparison of physical (melting point, TLC) and spectroscopic (UV, NMR) properties with published data. Application of the same reaction conditions to the purine derivatives adenosine (**3a**) and guanosine (**3c**) gave the 8-chloro nucleosides in good yield, thus giving the first successful preparation of 8-chloroguanosine (**4c**). In addition, when the reaction was applied to the potent antiviral agent 9-β-D-arabinofuranosyladenine (araA, **3b**) the product, 9-β-D-arabinofuranosyl-8-chloroadenine (**4b**), was obtained in good yield. Previous attempts to prepare 8-haloarabinoadenosine derivatives have been frustrated by the facile intramolecular displacement of the 8-halo moiety by the 2′-hydroxyl group to produce 8,2′-anhydro-8-oxy-9-β-D-arabinofuranosyladenine (**5**). The ease of this transformation was apparent when adsorption of **4b** onto silica gel, in the absence of any acid, followed by chromatographic separation led to **5** as the sole product, with no observable **4b** being eluted. Furthermore, treatment of **4b** with 1 M NH_4OH or 1 M NaOH gave **5** quantitatively (by TLC), in parallel to the observation that deblocking of 9-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-8-bromoadenine with base gives **5** as the only product.[18] Preparation of **4b** from **5** by ring-opening at C8 with HCl gave **4b** in only 10% yield.[19] It should be noted that reactions of MCPBA with **3a** or **3b** in the absence of HCl gave N^1-oxidation exclusively.[20]

The generality of the halogenation reaction described herein was demonstrated by preliminary experiments with HBr instead of HCl. Bromination occurred readily in both the pyrimidine and purine series in a manner analogous to the chlorination described above. However, we did not pursue this method of bromination because several facile high-yield preparations of 5-bromopyrimidine and 8-bromopurine nucleoside derivatives are already available.[5-11]

Precedent for the halogenation reaction described herein can be obtained by inspection of the literature which shows a related transformation in which 5-fluorouracil was reacted with concentrated HCl in the presence of H_2O_2 to produce the saturated adduct *dl*-5-chloro-5-fluoro-6-hydroxyhydrouracil.[21] Regeneration of the 5,6-double bond (by loss of H_2O) is not possible in this instance due to the fluorine substituent at C5.[21,22] Outside of the nucleoside field, Kumar and Kalra have described the use of H_2O_2 and HCl, in the presence of acetic acid, for the chlorination of selected ketones at carbon atoms adjacent to the carbonyl group.[23] Furthermore, Grossert and Chip have utilized $TiCl_4/CH_3COOOH$ for the chlorination of selected aromatic compounds.[24]

In summary, the new chlorination method described herein has several advantages over those currently available, namely, ready availability of starting materials, good to excellent yields of products, mild reaction conditions, short reaction times (less than 3 h), and facile workups. Access to some of the products described (e.g., **3b** and **3c**) is extremely difficult by previous methods. Application of this procedure to other systems is currently being investigated.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian HR-220 spectrometer operating in the CW or FT mode with Me_4Si as internal reference, and UV spectra were recorded on a Beckman Model 25 spectrophotometer. Elemental analyses were determined by Galbraith Laboratories. Evaporations were effected by using Büchi rotary evaporation under aspirator or mechanical oil pump vacuum at 40 °C or lower. TLC was performed on Merck silica gel 60 F-254 plates in solvent A

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($CHCl_3$–MeOH, 7:3) or solvent B ($CHCl_3$–MeOH–H_2O, 65:25:4) or on Merck cellulose F-254 plates in solvent C (2-propanol–NH_4OH–H_2O, 7:2:3). UV-absorbing compounds were detected by visualization under a UV lamp (254 nm). Column chromatography was carried out on Merck silica gel 60 (70–230 mesh) or on Dowex 1 × 2 (200–400 mesh; OH^- form). MCPBA was purchased from Aldrich and purified before use.[25] Dimethylacetamide and dimethylformamide were dried over BaO and distilled under reduced pressure.

5-Chlorouridine (2a).[12,13] Compound **1a** (0.244 g, 1.0 mmol) was dissolved in DMA (2 mL) with warming, 0.5 M HCl in DMA[26] (2 mL) was added, and the solution was cooled to 0 °C. MCPBA (0.277 g, 1.6 mmol) was then added over a period of 10 min (two portions), and the solution was stirred at room temperature for 2 h. TLC (solvent A) showed complete reaction. The solution was concentrated to ~2 mL, and H_2O (4 mL) was added. A white precipitate formed which was filtered off and washed with H_2O. The filtrate and washings were combined and extracted with Et_2O (3 × 3 mL) before being evaporated to dryness. The residue was evaporated from EtOH and then triturated with Et_2O to give a pure crystalline product which was filtered off to yield 0.252 g (90.4%) of **2a**.

5-Chlorocytidine (2b).[12,13] To a solution of **1b** (0.483 g, 2.0 mmol) in 0.5 M HCl in DMA[26] (5.0 mL) was added MCPBA (0.520 g, 3.0 mmol), and the solution was stirred at room temperature for 1 h. Additional MCPBA (0.100 g, 0.6 mmol) was then added, after a further 30 min the reaction mixture was concentrated to ~1 mL, and the oily residue so obtained was partitioned between Et_2O (50 mL) and H_2O (10 mL). The organic layer was washed once with H_2O, and the combined aqueous layers were backwashed with Et_2O, concentrated to small volume, and applied to a Dowex 1 × 2 (OH^- form) column (2.5 × 4.0 cm). This was developed first with H_2O (50 mL) and then with 50% aqueous MeOH. Fractions containing the required product were pooled and evaporated to dryness. Crystallization from MeOH gave 0.310 g (56%) of **2b**.

5-Chlorodeoxycytidine (2c). To a solution of **1c** (0.272 g, 1 mmol) in DMF (6 mL) was added 0.5 M HCl in DMF[26] (2.5 mL), followed by a solution of MCPBA (0.300 g, 1.7 mmol) in DMF (2 mL). After 2 h at room temperature, additional 0.5 M HCl in DMF (0.5 mL) and MCPBA (0.070 g, 0.4 mmol) were added, and the reaction was continued for a further 3 h. The clear reaction mixture was then evaporated to dryness, and traces of DMF were removed by coevaporation with xylene (2 × 3 mL). The residue was dissolved in MeOH (3 mL), and H_2O (20 mL) was added. A white precipitate formed which was filtered off and washed with H_2O. The filtrate was neutralized with 1 M NH_4OH and then evaporated to give a colorless gum. This material was absorbed onto silica gel (2 g) by evaporation to dryness from a methanolic solution and then placed atop a dry-packed silica gel column (15 g). The column was developed successively with 5% MeOH in $CHCl_3$ (250 mL), 10% MeOH in $CHCl_3$ (500 mL) and then 15% MeOH in $CHCl_3$ (500 mL). Fractions containing the required product were pooled and evaporated to dryness, and the residue was crystallized from MeOH/acetone to give 0.238 g (75.1%) of **2c**.

1-β-D-Arabinofuranosyl-5-chlorocytosine (2d).[13] Compound **1d**·HCl (0.300 g, 1.07 mmol) was dissolved in DMA (15 mL) with warming, and then the solution was cooled to room temperature. First 0.5 M HCl in DMA[26] (0.5 mL) and then MCPBA (0.300 g, 1.74 mmol) in DMA (2 mL) were added, and the solution was stirred for 1 h. The reaction mixture was then evaporated to dryness, and traces of DMA were removed by further evaporations from xylene (2 × 3 mL) and EtOH–xylene (2:3, 5 mL). The residue so obtained was dissolved in MeOH (2 mL), with warming, and this solution was added dropwise to H_2O (10 mL). A white precipitate formed instantly and was filtered off and washed with H_2O (10 mL). The combined filtrates were evaporated to dryness to give a stiff foam (after coevaporation from EtOH). This material was crystallized from 95% EtOH to give 0.250 g (83.9%) of **2d**.

8-Chloroadenosine (4a).[14,15] Compound **3a** (0.267 g, 1.0 mmol) was dissolved in 0.5 M HCl in DMA[26] (2.5 mL) with warming, and then the solution was cooled to room temperature. MCPBA (0.300 g, 1.74 mmol) in DMA (2 mL) was added, and the solution was stirred for 2.5 h. Additional 0.5 M HCl in DMA (0.5 mL) and MCPBA (0.070 g, 0.4 mmol) were then added, and the reaction was allowed to progress for an additional 1 h. The brown reaction mixture was then evaporated to dryness, and traces of DMA were removed by coevaporation from EtOH–xylene (1:2, 2 × 3 mL). The gummy residue so obtained was dissolved in MeOH (3 mL), and H_2O was added. A white precipitate was formed which was filtered off and washed with H_2O. The combined filtrate and washings were extracted with Et_2O (2 × 5 mL), the aqueous layer was concentrated to a small volume, silica gel (~ 2 g) was added, and the evaporation was then continued to dryness. This material was placed atop a dry-packed column (20 g) of silica gel and was developed first with 5% MeOH in $CHCl_3$ (500 mL) and then with 7% MeOH in $CHCl_3$. Fractions containing the required product were pooled and evaporated to dryness to give 0.151 g (50%) of **4a**. An analytical sample was obtained by crystallization from EtOH.

1-β-D-Arabinofuranosyl-8-chloroadenine (4b).[19] To a stirred solution of **3b** (0.300 g, 1.12 mmol) in 0.5 M HCl in DMA[26] (3.5 mL) was added a solution of MCPBA (0.300 g, 1.74 mmol) in DMA (2 mL). After 30 min, additional MCPBA (0.150 g, 0.87 mmol) was added and the stirring was continued for a further 1 h. The reaction was concentrated to a small volume, and H_2O (15 mL) was added. A white precipitate formed which was filtered off and washed with H_2O. The combined filtrate and washings were evaporated to dryness to give a gum which was dissolved in 90% aqueous MeOH (5 mL) and 1 M HCl (1.2 mL).[27] Silica gel (3 g) was added, and evaporation to dryness gave a powder which was placed atop a dry-packed silica gel column (25 g) developed first with 5% MeOH in $CHCl_3$ and then with 7% MeOH in $CHCl_3$. Fractions containing the required product were pooled and evaporated to dryness, and the residue so obtained was crystallized from EtOH containing a little 1 M HCl to give 0.168 g (48.5%) of **4b**·HCl as white crystals.

8-Chloroguanosine (4c). To a stirred solution of **3c** (0.566 g, 2.0 mmol) in 0.5 M HCl in DMA (4.4 mL) was added MCPBA (0.450 g, 2.6 mmol). After 20 min, additional MCPBA (0.100 g, 0.58 mmol) was added, and after a further 2 h the mixture was concentrated to ~1 mL. This residue was partitioned between H_2O and Et_2O, and the aqueous layer was then applied to a column (2.5 × 4.0 cm) of Dowex 1 × 2 (OH^- form). After being washed with H_2O (300 mL), the column was developed with 2% acetic acid, and fractions containing required product were pooled and evaporated to dryness. The residue was crystallized from 50% aqueous EtOH to give 0.266 g (39.6%) of **4c**.

8,2′-Anhydro-8-oxy-9-β-D-arabinofuranosyladenine (5).[19,28] To a stirred solution of **3b** (0.3 g, 1.12 mmol) in 0.5 M HCl in DMA[26] (3.5 mL) was added a solution of MCPBA (0.450 g, 1.74 mmol) in DMA (2 mL) (two 1-mL additions). The colored mixture was stirred overnight at room temperature and was then concentrated to a small volume. Water (15 mL) was added, the white precipitate so formed was filtered off and washed with water (20 mL), and the filtrate was evaporated to dryness. The TLC of the residue (silica gel, solvent A) showed two major spots, one of which comigrated with **4b**. The residue was dissolved in 90% MeOH (5 mL), silica gel (3 g) was added, and then the solvent was removed by evaporation in vacuo. The powder so obtained was placed on top of a dry-packed column of silica gel (25 g), and the column was developed successively with 5% MeOH in $CHCl_3$ (400 mL) and then 8% MeOH in $CHCl_3$. Careful examination of the eluents by TLC showed that there was now no spot corresponding to **4b**. Fractions containing the major product (**5**) were pooled and evaporated to dryness, and the residue was crystallized from DMF–ethanol to give 0.153 g (51.5%) of **5**. This product was identical by TLC with material obtained by treatment of **3b** with

(25) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, 1967, p 135.

(26) Solutions of HCl in DMA (or DMF) were prepared by bubbling anhydrous HCl into dry solvent at 0 °C. The solution was then allowed to rise to room temperature and the molarity checked by titration of an aliquot. The stock solution was then diluted to give a 0.5 M solution.

(27) If HCl was not added prior to the mixing with silica gel, then the major product was the cyclo compound **5**.

(28) M. Ikehara, T. Hada, and M. Kanedo, *Tetrahedron*, **24**, 3489 (1968).

1 M NH_4OH or 1 M NaOH.

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Registry No. 1a, 58-96-8; **1b**, 65-46-3; **1c**, 951-77-9; **1d**·HCl, 69-74-9; **2a**, 2880-89-9; **2b**, 25130-29-4; **2c**, 32387-56-7; **2d**, 17676-65-2; **3a**, 58-61-7; **3b**, 5536-17-4; **3c**, 118-00-3; **4a**, 34408-14-5; **4b**·HCl, 77415-35-1; **4c**, 2104-68-9; **5**, 13089-44-6.

Sulfamides: Polar Aprotic Solvents Compatible with Grignard Reagents

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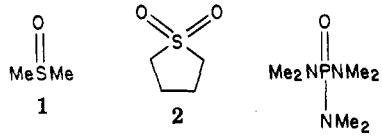
A polar aprotic solvent[2] has a reasonably high dielectric constant and a dipolar function with an exposed negative end but a buried positive end. As a result, it is an effective specific solvating agent for cations but not for anions. Anions in such solvents are less solvated and hence more reactive, often by many orders of magnitude, than in polar protic solvents. Polar aprotic solvents are used widely in physical chemical studies and in synthetic applications in which anion activity is important. Industrial uses for some of these solvents also are due to their considerable solubilities for certain gases and polymers and greater solubilities for aromatic than for aliphatic hydrocarbons.[3]

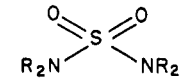
Polar aprotic solvents should be useful with organometallic compounds. For example, coordination by a polar aprotic solvent with the metal of a polar organometallic compound could increase the polarity of the carbon–metal bond. Unfortunately, polar organometallic compounds often react with these solvents. For example, Grignard reagents add to the carbonyl group of dimethylformamide to give aldehydes, reduce dimethyl sulfoxide (1), and abstract an α-hydrogen from sulfolane (2).[4]



1 2 3

Hexamethylphosphoramide (HMPA, 3) is the only polar aprotic solvent that has been used extensively with Grignard reagents.[5,6] Effects of HMPA used either as a solvent for organomagnesium compounds or as an additive to their solutions in other solvents are often large. However, even HMPA has limitations. Its stability is less than would be desirable. At temperatures well below ambient, organolithium compounds attack HMPA and are destroyed.[7] Even Grignard reagents are not completely stable in contact with HMPA.[8] Moreover, potential health hazards are associated with the use of HMPA.[9]

We thought that tetraalkylsulfamides (4) would be



4a, R = Me
b, R = Et

reasonable possibilities for use as polar aprotic solvents that could have considerable stability toward polar organometallic compounds.[10,11] The functional group, combining the sulfonyl and dialkylamino groups found in some commonly used polar aprotic solvents, would be expected to impart characteristic polar aprotic solvent properties, and it has been reported[12] that **4b** is hydrolyzed in aqueous base only with great difficulty.

Our observations with sulfamide **4b** are encouraging[13] and suggest that compounds with sulfamide functions may be useful as solvents for organometallic compounds and for other strongly basic and nucleophilic reagents. Solutions of ethylmagnesium bromide (90%), propylmagnesium bromide (80%), isopropylmagnesium chloride (87%), and phenylmagnesium bromide (40%) in **4b** were prepared directly from organic halides and magnesium at ambient temperature. The ethyl and propyl Grignard reagent solutions showed no signs of decomposition (^{1}H NMR observations) at ambient temperature during a 3-week period. A hexane solution (25%) of diethylzinc to which 2 equiv of **4b** was added also seemed to be stable. Even attack by an organolithium compound was not rapid. The half-life at ambient temperature of a 2.0 M hexane solution of butyllithium to which 2 equiv of **4b** was added was about 1 h. Presumably, stability would be even greater at lower temperature.

As solvents, sulfamides probably will resemble sulfolane rather than the more exciting HMPA. The effectiveness of polar aprotic solvents parallels roughly the chemical shifts of the ^{1}H NMR absorption of $CHCl_3$ at infinite dilution in the solvents (compared to the chemical shift

(1) Undergraduate research participant.
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(6) It has been mentioned that tetramethylurea is not attacked by Grignard reagents (Lüttringhaus, A.; Dirksen, H. W. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 260), but we have found only one reference (Brodzki, D.; Wakselman, C.; Wartski, L. *Bull. Soc. Chim. Fr.* **1972**, 1429) to its use as a solvent for organomagnesium compds, and that for methyl reagents, which are known to be relatively unreactive. Tetraalkylureas and *N,N*-dialkyl amides have been found to be useful solvents for reactions involving alkali metals: Sakurai, H.; Kondo, F. *J. Organomet. Chem.* **1976**, *117*, 149; Young, C. A.; Dewald, R. R. *J. Chem. Soc., Chem. Commun.* **1977**, *188*; *J. Am. Chem. Soc.* **1979**, *101*, 2884; Sowinski, A. F.; Whitesides, G. M. *J. Org. Chem.* **1979**, *44*, 2369.
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(10) For a brief review of sulfamides and sulfurous diamides, see: Appel, R.; Kohnke, J. *Method. Chim.* **1978**, *7*, 743.
(11) We have no information about toxicities of sulfamides.
(12) Yamaguchi, H.; Nakano, K. *Hiroshima Daigaku Kogakubu Kenkyu Hokoku* **1972**, *21*, 23; *Chem. Abstr.* **1973**, *79*, 65420. Also see: Spillane, W. J.; Barry, J. A.; Heaphy, W. A.; Scott, F. L. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1974**, *29*, 702.
(13) Sulfamide **4a**, an obvious choice for study, is a solid (mp 73 °C) at ambient temperature and must be used with other solvents.

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