I. ALKYLATING AGENTS CONTAINING A QUATERNARY NITROGEN GROUP

II. RELATIVE NUCLEOPHILICITY. METHYLATION OF ANIONS IN AQUEOUS MEDIA

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FOREWORD

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Alkylating Agents Containing a Quaternary Nitrogen Group

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Received June 27, 1969

A series of 14 new, water-soluble alkylating agents was synthesized. The structures contain an alkylsulfonate group as the alkylating function and a quaternary ammonium salt group attached to a hydrocarbon backbone.

A large body of literature exists on the blocking or inhibition of the enzyme acetylcholinesterase by various phosphorus poisons. Thus, alkyl methylphosphono-fluoridates become attached to the enzyme site, presumably by phosphorylation of an O-serine component of the enzyme protein. The result is that the normal enzyme function of hydrolyzing acetylcholine is prevented. Removal of the phosphorylated inhibition has been successfully accomplished by various oxime "reactivators" such as 2-pyridinealdoxime methiodide (2-PAM). Reactivation may be complicated, however, by a phenomenon known as "aging" whereby the alkyl group of the phosphonate inhibitor is cleaved, presumably generating an oxygen ion. The net result is

1. This work was performed under Edgewood Arsenal Contract DA-19-108-AMC-292-A1

that oximes such as 2-PAM are not effective. To clarify more fully the character of the aged, inhibited enzyme, realkylation of the phosphonate anion would be of great interest, and our attention was directed to the design of alkylation agents capable of functioning in biological media.

Phosphonate salts are known to be poor nucleophiles in alkylation reactions, presumably because the anions are weakly basic (conjugate acids have pKₐ values approximately 2). Accordingly, a highly reactive alkylation agent was required and an ester of a strongly acidic anion was an ideal candidate. This led to the design of a model series in which the active alkylation moiety is an alkylsulfonate group with the incorporation in the structure of a quaternary nitrogen to provide potential binding to the enzyme site and water solubility in neutral media. In view of this, the synthesis of a series of structures such as (CH₃N⁺CH₃)₂SO₃CH₂X⁻

was initiated, where n is 2-6 and X⁻ is an inert anion such as perchlorate. Acquisition of a successful procedure led to modified structures wherein the alkylene chain was branched, the trimethylammonium group was replaced by triethylammonium and pyridinium groups, methyl was replaced by an ethyl alkylating group, and a second alkylation group and/or a second quaternary ammonium moiety were introduced. In addition, the alkylsulfonate group was successfully introduced on the pyridine ring, i.e., 3-(methylsulfonate)-1-methylpyridinium perchlorate. This first paper reports the results of the synthetic program. Kinetic data on the alkylation of phosphonate anions and other biologically important anions in aqueous media are reported in the following paper.

Results and Discussion

Work was initiated with unsuccessful attempts to prepare the propane analog, a methyl 3-(trimethylammonium)propylsulfonate salt, using conventional procedures. Treatment of methyl 3-iodopropane sulfonate with trimethylamine in ether solution resulted in alkylolation of the amine, forming the tetramethylammonium salt of 3-iodopropene sulfonic acid. The same reaction in acetoneitrile gave tetramethylammonium iodide and the inner salt, 3-(trimethylammonium)propyl sulfobetaine. The evidence indicated that the desired alkylation agent was formed in acetoneitrile, but was rapidly attacked by the excess amine to form a quaternary iodide and the stable inner salt. Alternatively, methyl iodide which would be converted to the quaternary iodide could be formed by internal alkylation.

Insamuch as 3-(trimethylammonium)propyl sulfobetaine was rapidly prepared from the commercially available 3-hydroxypropanesulfonic acid sulfone by ring opening with trimethylamine, attempts were made to convert the sulfobetaine to the sulfonium chloride with phosphorus pentachloride and chlorosulfonic acid, or with thionyl chloride and catalytic quantities of dimethylformamide. Formation of crude sulfonium chloride was demonstrated in each instance by isolation of a sulfonamide, but treatment with methoxide ion gave mixtures in which only the inner salt could be isolated.

In the third and successful approach, the n-propane sulfobetaine was treated with dimethyl sulfate at reflux (185-190°) for 3 hr to yield a crude methyl sulfonate salt. The latter was then converted to the stable perchlorate salt by passage in methanol over a Dowex-1 (hydroxide) ion-exchange column at -70° and neutralization of the effluent with perchloric acid.

(C₂H₅O₂)₂SO₃M⁺ + (CH₃O)₂SO₄⁻ →

CH₃⁺ + (CH₃)₂SO₃⁻ + SO₄²⁻ + H⁺ + CH₃CO₂⁻ + [Cl⁻]

The method proved general and was applied to all alkylation agents reported herein. In a number of cases, the column technique could be replaced by utilizing a solution of barium perchlorate in acetone, or methanol, to convert the crude methane sulfonate salts to the perchlorate salts.

The most active agent was 3-(methylsulfonate)-1-methylpyridinium perchlorate. This was successfully prepared from both 3-pyridinesulfonic acid and 3-pyridinium-1-methyl sulfobetaine. Under comparable conditions, the yield from the sulfonic acid was 6-10%, whereas the sulfobetaine gave only a 4% yield. The reaction with 3-pyridinesulfonic acid was optimized to give a 20% yield. 3-(Ethylsulfonate)-1-ethylpyridinium perchlorate was prepared in 30% yield using diethyl sulfite. However, all attempts to prepare 2- and 4-(methylsulfonate)-1-ethylpyridinium perchlorate failed. Interestingly, it was discovered that both the 2- and 4-pyridinium sulfobetaines were converted to the 2- and 4-methoxy-1-ethylpyridinium perchlorate by passage in 70% methanol-water (v/v) over the Dowex-1 (hydroxide) column and neutralization of the effluent with perchloric acid.

\[ \text{CH}_3\text{O} + \text{HClO}_4 \rightarrow \text{CH}_3\text{O}^+ + \text{ClO}_4^- \]

The precursors sulfobetaines are stable, high-melting (230-367°C), neutral, and water-soluble inner salts, insoluble in organic solvents. They were prepared by (a) treatment of α-haloalkyl sulfonic acids or their salts with tertiary amines; (b) treatment of α-tertiary amine alkyl halides with sodium sulfite; or (c) ring opening of the corresponding cyclic sulfones with tertiary amines. The alkylation agents are soluble in polar solvents such as water, acetone, and acetoneitrile and slightly soluble in methanol. All new compounds were characterized by elemental analysis, infrared spectra, and, in some cases, nmr spectra. The alkylation agents are listed in Table 1 with melting point and yield data.

Experimental Section

Compound 3-14 were prepared from the precursor sulfobetaine, generally via the cyclic sulfone. The general procedure presented below is representative of the series with additional details added under the specific compound, as required.

3-(Methylsulfonate)-1-methylpyridinium perchlorate (1) and 3-(methylsulfonate)-1-ethylpyridinium perchlorate (2) were prepared directly from 3-pyridinesulfonic acid and dialkyl sulfite.
The sulfobetaine was treated with dimethyl sulfate by the standard procedure to give crude triethyl compound, mp 117-119°. Recrystallization from acetone-ether gave an analytical sample, mp 119-120°.

Anal. Calcd for CH₃N·CINO·8Cl: C, 43.05; H, 7.06; Cl, 35.46; S, 9.48. Found: C, 42.85; H, 7.08; S, 9.36.

The sulfobetaine was heated with excess dimethyl sulfate for 3 hr at 65-75° to give the title compound (90%), mp 117-119°. Recrystallization from acetone-ether gave an analytical sample, mp 117-119°.

Anal. Calcd for CH₃N·CINO·8Cl: C, 55.22; H, 7.12; N, 4.14; S, 9.49. Found: C, 54.16; H, 7.40; N, 3.87; S, 9.65.

Methyl 3-trimethylammonium perchlorate (15).—3-Trimethylammonium perchlorate (10).—Butane sulfonate (12).—Butane sulfonate (12).—Butane sulfonate (12).

Anal. Calcd for C₈H₂₆N·ClO₄·S: C, 54.20; Cl, 4.99; N, 3.80. Found: C, 54.49; Cl, 4.99; N, 3.79.

The sulfobetaine was purified from ethyl acetate with ether, dissolved in methanol, and passed over a 100-x-2 column. The ester, 3-trimethylammonium perchlorate (15).—Butane sulfonate (12).

Anal. Calcd for C₈H₂₆N·ClO₄·S: C, 54.20; Cl, 4.99; N, 3.80. Found: C, 54.49; Cl, 4.99; N, 3.79.

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Anal. Calcd for C₈H₂₆N·ClO₄·S: C, 54.20; Cl, 4.99; N, 3.80. Found: C, 54.49; Cl, 4.99; N, 3.79.
The new spectrum was compatible with the assigned structure. The aceto-soluble portion was recrystallized to yield 1-methyl-3-pyrrolidinyl sulfonate (100 mg, 46%), mp 251-253°C. The sulfonate was prepared also directly by treating 3-pyrrolidinocrotonic acid with a tenfold weight excess of dimethyl sulfate at 160-170°C for 20 hr. The solid product which separated was recrystallized (twice from water-methanol to yield 85% yield, mp 355-358°C.

Anal. Caled for Cl8H32NO8: C, 41.61; H, 4.07; N, 8.09. Found: C, 41.77; H, 4.23; N, 8.18.

Treatment of 1-methylpyrrolidinyl sulfonate with dimethyl sulfate in the same manner as with 3-pyrrolidinocrotonic acid gave only a 4% yield of compound 1.

B. Barium Perchlorate Method—Extensive studies led to the following optimum procedure. 3-Pyrrolidinocrotonic acid (1 g) was heated for 6 hr with dimethyl sulfate (110 ml) at 105°C, or slightly below reflux. Excess dimethyl sulfate was removed by extraction with anhydrous ether. The syrropy residue was dissolved in 25 ml of acetone and the solution was concentrated, diluted with water, and filtered. The solid crude product was recrystallized from acetone-ether. The title compound (63%), extraction with anhydrous ether. The ropy residue was triturated with ether. The residual gummy solid, 3,9-ethyl-4-(trimethylammonium)octane (11), was triturated with benzene-methanol, and the solution was concentrated to a syrup which separated to yield 76% of the title compound (74°C). After recrystallization from acetone-ether, the title compound was obtained.

Anal. Caled for Cl8H24NO4: C, 41.27; H, 6.23; N, 10.18. 4. Ethyl-4-(trimethylammonium)octane Sulfonate (14)—4-Hydroxyhexanenitrile acid, prepared from 1-acetoxy-4-chlorobutane by reaction with aqueous sodium sulfite, was cyclized at 150°C at 1 atm pressure to yield 4-ethyl-butanonitrile, bp 102-105°C (1 atm), according to the method of Pellerin.26 The overall yield from 1-acetoxy-4-chlorobutane was 32%. 4-Ethylbutanone was heated with trimethylamine in a sealed tube at 110°C for 12 hr. The hydroscopic product, 4-ethyl-4-trimethylammonium butane sulfonate (15%), after recrystallization from ethanol-ether, had mp 228-230°C. The sulfonate was converted to the title compound (63%).

Anal. Caled for Cl8H34NO4: C, 43.54; H, 7.16; N, 1.17*. Found: C, 35.5; H, 0.59; N, 4.12; S, 9.16.

4-Methyl-3-monomethoxyhexane-1-trimethylamine (12)—4-Methyl-3-monomethoxyhexane (11) was converted to the title compound (63%), extraction with anhydrous ether. The title compound, mp 238-240°C, slightly below theoretical, was triturated with ether. The residual gummy solid, 3-(Methylalkylfumarate)-1-methylpyridinium Perchlorate (1). Anlm. Calcd for C14H18NO4: C, 36.66; H, 5.02; N, 5.31; S, 10.99.

Anlm. Calcd for C18H28NO4: C, 35.1% (26°C), 35.0% (0°C), 35.5% (25°C). 3-Acetoxy-1-methylpyridinium Perochlorate (2).—3-Acetoxy-trimethylamine was prepared as above, was refluxed with dimethyl sulfate for 2 hr. After cooling, the solution was concentrated to near dryness, diluted with absolute ethanol, and filtered. The title compound was obtained.

Anlm. Calcd for C18H20NO4: C, 35.5% (26°C), 35.0% (0°C), 35.5% (25°C). 3-Acetoxy-trimethylamine was prepared as above, was refluxed with dimethyl sulfate for 2 hr. After cooling, the solution was concentrated to near dryness, diluted with absolute ethanol, and filtered. The title compound was obtained.

Anlm. Calcd for C18H20NO4: C, 35.5% (26°C), 35.0% (0°C), 35.5% (25°C). 3-Acetoxy-trimethylamine was prepared as above, was refluxed with dimethyl sulfate for 2 hr. After cooling, the solution was concentrated to near dryness, diluted with absolute ethanol, and filtered. The title compound was obtained.

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Anlm. Calcd for C18H20NO4: C, 35.5% (26°C), 35.0% (0°C), 35.5% (25°C). 3-Acetoxy-trimethylamine was prepared as above, was refluxed with dimethyl sulfate for 2 hr. After cooling, the solution was concentrated to near dryness, diluted with absolute ethanol, and filtered. The title compound was obtained.

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Anlm. Calcd for C18H20NO4: C, 35.5% (26°C), 35.0% (0°C), 35.5% (25°C). 3-Acetoxy-trimethylamine was prepared as above, was refluxed with dimethyl sulfate for 2 hr. After cooling, the solution was concentrated to near dryness, diluted with absolute ethanol, and filtered. The title compound was obtained.

Anlm. Calcd for C18H20NO4: C, 35.5% (26°C), 35.0% (0°C), 35.5% (25°C). 3-Acetoxy-trimethylamine was prepared as above, was refluxed with dimethyl sulfate for 2 hr. After cooling, the solution was concentrated to near dryness, diluted with absolute ethanol, and filtered. The title compound was obtained.
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**Anal. Caled for CH₂CONO₂·H₂O: C, 25.58; H, 5.72; Cl, 12.58; N, 4.37; S, 11.28. Found: C, 25.84; H, 5.75; Cl, 12.54; N, 4.96; S, 11.20.**

**Preparation of 2- and 4-(Methylammonium)-1-methylpyridinium perchlorates.** 2-Hydropyridine was converted to 2-mercaptopyridine in 85% yield, yellow azealine, mp 120-124° (from ethanol), the melting point of Thirlh.**

**The mixture was heated with methanol and passed through Dowex-1 (hydroxide) column at 70°, the mixture was triturated with hexane and washed with acetone-ether to give the title compound (60%) of crude melonate. The solution was stirred overnight. The mixture was filtered and the precipitate was washed with ether and dried to give crude product (3.4 g, 14.4 mmol) in benzene (30 ml).**

Methyl iodide (1.08 g, 4.14 mmol) in benzene (30 ml) was added dropwise to a stirred solution of the diazeine (2.0 g, 14.4 mmol) in benzene (30 ml). The solution was stirred for 1 h in air. The precipitate was washed with ether and dried to yield crude product (2.5 g, mp 141-148°). The latter was dissolved in ethanol and the precipitate was washed with ether and dried to give 2- and 4-pyridylamine, methyl iodide (2.68 g, 70%), mp 140-147°.

**The methyl iodide (1.08 g, 4.14 mmol) in benzene (30 ml) was added dropwise to a stirred solution of the diazeine (2.0 g, 14.4 mmol) in benzene (30 ml). The solution was stirred for 1 h in air. The precipitate was washed with ether and dried to yield crude product (2.5 g, 141-148°). The latter was dissolved in ethanol and the precipitate was washed with ether and dried to give 2- and 4-pyridylamine, methyl iodide (2.68 g, 70%), mp 140-147°.

**Anal. Caled for CH₂CONO₂·H₂O: C, 41.61; H, 4.07; N, 8.08. Found: C, 41.84; H, 4.17; N, 7.50; S, 11.16.**

**The mixture was heated with methanol and passed through Dowex-1 (hydroxide) column at 70°, the solution was stirred overnight. The mixture was filtered and the precipitate was washed with ether and dried. Crude 3-bis(1,4-dimethylaminobutyl)pyridinium acetate (8.0 g, 95%), mp 201-202°, was prepared by recrystallization twice from methanol-acetone, mp 138-139°.**

**Preparation of Methyl 3,3'-Bis(1,4-dimethylaminobutyl)propionate Sulfonate (17).** Sulfonate (40.3 g, 66 mmol) and propanol (7.3 g, 0.11 mol) in benzene (43 ml). The solution was stirred at room temperature and then refluxed for 1 h. The precipitated betaine was filtered and washed with benzene to give the title compound (45%).

**Preparation of Methyl 3,3'-Bis(dimethylaminomethyl) Perchlorate (18).** Sulfonate (13.5 g, 66 mmol) and propanol (7.3 g, 0.11 mol) in benzene (43 ml). The solution was stirred at room temperature and then refluxed for 1 h. The precipitated betaine was filtered and washed with benzene to give the title compound (45%).

**Preparation of Methyl 3,3'-Bis(dimethylaminomethyl) Perchlorate (18).** Sulfonate (13.5 g, 66 mmol) and propanol (7.3 g, 0.11 mol) in benzene (43 ml). The solution was stirred at room temperature and then refluxed for 1 h. The precipitated betaine was filtered and washed with benzene to give the title compound (45%).

**Preparation of Methyl 3,3'-Bis(dimethylaminomethyl) Perchlorate (18).** Sulfonate (13.5 g, 66 mmol) and propanol (7.3 g, 0.11 mol) in benzene (43 ml). The solution was stirred at room temperature and then refluxed for 1 h. The precipitated betaine was filtered and washed with benzene to give the title compound (45%).
The product was purified further by trituration three times
with boiling acetone. The aecious-soluble portion was filtered
through Celite and ether was added to the filtrate. Compound:
10 separated on slow cooling; mp 105-106.57, 75% recovery.
Anal. Calcd for C\textsubscript{25}H\textsubscript{47}N\textsubscript{3}O: C, 53.75; H, 5.70; N
2.35. Found: C, 53.01; H, 5.30; N, 2.45.

Registry No.—1, 21870-83-5; 2, 21884-02-0; 3, 21864-93-7; 4, 21864-94-8; 5, 21864-95-9; 6, 21864-96-0; 7, 21864-97-1; 8, 21864-98-2; 9, 21864-99-3; 10, 21865-00-9; 11, 21865-01-0; 12, 21865-02-1; 13, 21865-03-2; 14, 21865-04-3; 15, 21865-05-4; 16, 21865-06-5; 17, 21865-15-6; 18, 21865-16-7; 3-(trimethylammonium)propane sulfobetaine, 21865-17-3; 3-(trimethylammonium)propane sulfobetaine, 1897-02-0; 3-(pyridinium)propane sulfobetaine, 15471-17-7; 3-(trimethylammonium)-1,1,3-trimethylpropane sulfobetaine, 21865-20-3; 3-(pyridinium)-1,1,3-trimethylpropane sulfobetaine, 21865-21-4; 4-(triethylammonium)butane sulfobetaine, 21870-42-6; 4-(pyridinium)butane sulfobetaine, 21870-43-7; 4-ethyl-4-(trimethylammonium)butane sulfobetaine, 21870-44-8; 4-ethyl-4-(pyridinium)butane sulfobetaine, 21870-45-9; 6-(trimethylammonium)hexane sulfobetaine, 21870-46-0; 1-methyl-3-pyridinium sulfobetaine, 21870-47-1; trimethyl taurine, 7465-57-8; 2-methoxy-1-methylpyridinium perchlorate, 21870-49-3; 1-methyl-2-pyridinium sulfobetaine, 4329-93-5; 4-methoxy-1-methylpyridinium perchlorate, 21870-51-7; N,N,N',N'-tetramethylbutylenediamine, 111-51-3; 4-(trimethylammoniumiodide)-1-dimethylaminobutane, 21870-53-9; +aza-4,4-dimethyl-8-trimethylammonium iodide octane sulfobetaine, 21870-54-0; 3,3'-di(1,1-tetramethylammoniumbutane)propane sulfobetaine, 21870-55-1.
Relative Nucleophilicity. Methylation of Anions in Aqueous Media

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Received June 27, 1969

Alkylation rate data were obtained for 16 anion nucleophiles in aqueous media at 25° (and 37°) and constant salt concentration using 1-methyl-3-(methylsulfonate)pyridinium perchlorate as the alkylating agent-substrate. The data at 25° are presented in terms of log $k_1/k_2$ and the Swain and Scott equation is employed to obtain the substrate constant, $s$ (oms1). Nucleophilic constants, $a$, are calculated and compared with published values for 12 anions, and new constants were determined for four phosphonate ion species.

The synthesis of a series of water-soluble alkylating agents has been described. A pyridine analog, 1-methyl-3-(methylsulfonate)pyridinium perchlorate, representing the most reactive agent of the series, was used as substrate, in the work reported herein, to measure nucleophilic constants by the Swain and Scott method.

This alkylating agent, in common with other members of the series, solvolyzes in water to form methanol, hydronium ion, perchlorate ion, and a stable, unreactive, water-soluble sulfobetaine. The alkylation of an anion results in the formation of the methylated anion, perchlorate ion, and the sulfobetaine. The equation for these (simultaneous) reactions is as follows, where $k_1$ is the solvolysis rate constant and $k_2$ is the second-order anion alkylation rate constant.

$$
\text{SO}_3\text{CH}_3 + \text{CH}_3\text{OH} + \text{H}^+ + \text{ClO}_4^- \rightarrow \text{CH}_3\text{CH}_2\text{OH} + \text{CH}_3\text{SO}_3^- + \text{ClO}_4^-$$

The ratio of $k_1/k_2$ and $k_3$ is determined conveniently in separate experiments in a pH Stat. Hydronium ion is not generated in the anion alkylation reaction, whereas it is a product of the competing solvolysis reaction. Accordingly, the reduction in the quantity of hydronium ion liberated at time $t$, relative to solvolysis in the absence of anions, is a measure of the extent of alkylation at time $t$. Mathematical treatment leads to the following general expression.

$$
k_3/k_2 = 2.3 \log \frac{[S_0]/[S_1]}{[H^+]}
$$

In this equation, $[S_0]$ is initial concentration of anion and $[S_1]$ is the concentration at time $t$, usually taken at infinity. The term $[H^+]$ is the molar hydronium ion formed by hydrolysis at time $t$; it is equal to the initial molar concentration of agent multiplied by the mole fraction of agent hydrolyzed.

The alkylation of 16 anion nucleophiles was studied kinetically in water at 25° (and 37°) and pH 7.0 with certain exceptions. The system was adjusted to 0.1 M in total salt; this is the sum of the agent and anion concentrations with sodium perchlorate added if required. The ratio of $k_1/k_2$ is salt concentration dependent, decreasing with increasing salt concentration. For three sluggish nucleophiles, data were taken more conveniently at 0.5 M salt and extrapolated to 0.1 M salt.

The observed ratios $k_1/k_2$ are multiplied by 55.4, the molar concentration of water, to give $k_3/k_2$. A conventional Swain and Scott treatment is based on the equation $\log k_1/k_2 = \omega n$, where $\omega$ is the anion nucleo-
Table I  
RELATIVE NUCLEOPHILICITY. Swain and Scott Method3  
substrate: 1- methyl-3-(methylsulfonyl)pyridinium perchlorate (25°, 0.1 M total salt, pH 7.0)  

<table>
<thead>
<tr>
<th>Anion</th>
<th>k/kₑ</th>
<th>kₑ/k₀</th>
<th>log kₑ/k₀</th>
<th>0.1 M</th>
<th>0.01 M</th>
<th>0.001 M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrate</td>
<td>0.20</td>
<td>11</td>
<td>1.0</td>
<td>1.0</td>
<td>1.4</td>
<td>1.03</td>
</tr>
<tr>
<td>p-Nitrophenyl</td>
<td>0.67</td>
<td>6.4</td>
<td>2.8</td>
<td>1.0</td>
<td>1.4</td>
<td>1.03</td>
</tr>
<tr>
<td>Methylophosphonate</td>
<td>0.27</td>
<td>15.0</td>
<td>1.18</td>
<td>1.7</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Isopropyl</td>
<td>0.57</td>
<td>31.8</td>
<td>1.50</td>
<td>2.1</td>
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<tr>
<td>Methylophosphonate</td>
<td>0.70</td>
<td>35.8</td>
<td>1.60</td>
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<td>Iodide</td>
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<td>7.1</td>
<td>6.4</td>
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</table>

* All except acetate, 7.1; bicarbonate, 8.3; and chloroacetonephosphonate, 7.0 (equivalence point). * Calculated from s = 0.715 (see footnote 4). * All values from Swain and Scott, except nitrate. * Bromide ion taken as standard; s = 3.6.4

A plot of the log kₐ/kₑ vs. n is employed normally to determine the slope, s, the substrate constant. In the present study, a plot of log kₐ/kₑ vs. the published nucleophilic constants3 for chloride, bromide, and iodide ions is linear within 0.02 log units. Accordingly, bromide ion (n = 3.65) was selected as standard to establish the substrate constant s as 0.715, and the nucleophilic constants listed in Table I were calculated by dividing log kₐ/kₑ by 0.715. The value of s of 0.715 for 1-methyl-3-(methylsulfonyl)pyridinium perchlorate is comparable in magnitude with other sulfonyl ester, ethyl p-toluenesulfonyl (0.66).1

The alkylation of isopropyl methylophosphonate anion was confirmed by nmr and product isolation studies.

At 25°, with bromide ion as standard, the slope was 0.702, reflecting the decrease in kₐ/kₑ to 9.6 M⁻¹ (from 10.9 M⁻¹ at 25°). Nucleophilic constants for nine anions were in agreement at those observed at 25° within 0.1 log unit or less.

Experimental Section

A recording Sargent pH-stat with thermistor temperature control (0.1°) was used. Solution volumes were 10-15 ml, 10⁻¹⁴ M in chloride, using 0.02-0.08 M sodium hydroxide as titrant with a nitrogen sweep. Sodium perchlorate was used electrolyte to adjust the total salt concentration to 0.1 M. The infinity concentration of hydrox-ιn ion was adjusted for 60% of the volume of the titrant. Five or more runs were made for each nucleophile in most cases and the results are reported; the number of significant figures is warranted by the precision of the data under study. Nucleophilic constants expressed to two significant figures have a probable error of 0.1 log unit. Solvolysis rate constants for 1-methyl-3-methylsulfonate pyridinium perchlorate were determined in water (0.1 M sodium perchlorate) at pH 7.0 at 25°. The kₐ was 8.18 (±0.10) × 10⁻¹⁴ sec⁻¹ at 25°, kₒ is 3.07 (±0.12) × 10⁻¹⁴ sec⁻¹. The rate decreases with increasing salt concentration (see below).

Phosphonate and Thio phosphonate.—The alkylation of isopropyl methyl phosphonate was studied at 25°, 0.1 M in anion and 5 × 10⁻¹⁴ M in substrate. The ratio of kₐ/kₑ was 0.56 M⁻¹ at 0.5 M salt, the ratio was 0.41 M⁻¹. For p-nitrophenyl methylphosphonate, 0.5 M in anion, the ratio of kₐ/kₑ was 0.19 M⁻¹. The isopropyl methylphosphonate was extensively studied also at 37° and the ratios varied with phosphonate concentration as follows: 0.7 M, 0.23; 0.5 M, 0.25; 0.17 M, 0.37. A comparative study of isopropyl methylphosphonate was made with five analogous agents at 37°, 0.70 M in phosphonate and 7 × 10⁻¹⁴ M in agent; the values of kₐ/kₑ ranged from 0.26 to 0.29, or constant within experimental error. To establish a nucleophilic constant for a phosphonate diazonium, chloroacetylphosphonic acid of high purity was used. The study was made at the equivalence point (pH 9.0), pKₐ = 2.14 and pKₐ = 6.41, as determined in water at 25°. In a system 0.5 M in diazonium, the ratio of kₐ/kₑ at 25° was 2.51, corrected to 7.28 at 0.1 M salt concentration. The alkylation of ethyl methylphosphonate anion was studied at 25°, 17.2 × 10⁻¹⁴ M in substrate and 4.95 × 10⁻¹⁴ M in thio phosphonate adjusted to 0.1 M total salt with sodium perchlorate. The ratio of kₐ/kₑ = 146 M⁻¹; at 37°, two r-n gave the value of 1.16 and 122 M⁻¹.

Other Anions.—Bromide ion, the standard, was studied at 37° over a range of total salt concentration. The observed values for kₐ/kₑ (M⁻¹), a function of total salt concentration (substrate plus bromide ion), are as follows: 0.026 M, 3.4; 0.005 M, 3.2; 0.100 M, 3.1; 0.125 M, 3.0; 0.020 M, 2.8; 0.251 M, 2.6. Alkylation of thiophosphonate exceeded 60% even at a 1:1 molar ratio of substrate to anion; the results were reproducible within 0.1 log unit although the absolute error may be greater. Bicarbonate ion was studied at pH 8.30 over a wide range of molar ratios of bicarbonate to substrate; kₐ/kₑ values ranged from 21 to 25 M⁻¹ increasing in this case with increasing salt concentration. Alkylated were determined at pH 9.0 where the system appeared to be more stable than at pH 7.0. Thio cyanate ion was studied at pH 7.0 with good reproducibility. Chloride ion was checked independently using a nitrolic agent, methyl 3-(trimethylammonium) phosphonate, saline, both in the pH-stat and by a sample-withdrawal titration technique.

The less reactive nucleophiles (the first five anions of Table I) were studied in water at 25°, 0.5 M in anion and 10⁻¹⁴ M in substrate. The rates, kₐ/kₑ, were as follows (M⁻¹); nitrate, 0.17; p-nitrophenyl methylphosphonate, 0.19; isopropyl methylphosphonate, 0.41; fluoride, 0.21; sulfite, 1.02. Isopropyl methylphosphonate and sulfite ions were studied at a concentration of 0.1 M in anion plus agent to give kₐ/kₑ ratios of 0.57 and 1.44 M⁻¹. This corresponds, in both cases, to a factor of 1.4 in

between 0.5-0.1 M. This factor was used to estimate $k_b/k_1$ at 0.1 M ($k_1$ salt for the other three less reactive anions (see bromide ion data above).

The ratios of $k_b/k_1$ ($M^{-1}$), listed in Table I, were determined at 25°C. At 37°C, corresponding data (0.1 M total salt) for nine anions are as follows: isopropyl methylphosphonate, 2.0; fluoro-
ride, 2.1; chloride, 3.6; acetate, 3.82; bromide, 3.80 (standard); azide, 4.7; 3-bocyanate, 4.88; ethyl methylthiophospho-
phonate, 5.5; iodide, 5.91.

Nmr Studies—Nmr studies were made of the solvolysis of 3-sister agent, methyl 3-(trimethylammonium perchlorate)propane sulfonate, in deuterium oxide, and the alkylation of sodium isopropyl methylphosphonate was studied in chloroform and deuterium oxide. All studies were carried out in an nmr tube using a Varian DP-60 operating at 60 MHz. Hydrolysis of a saturated solution (7%) of the agent in deuterium oxide was followed by the disappearance of the signal due to protons on the SOCl$_2$ group at 6 6.1 and the appearance of the signal due to methanol at 6 3.6. Alkylation of isopropyl methylphosphonate anion was studied with the same substrate, but the substrate anion was isopropyl methylphosphonate instead of perchlorate.

The chloroform solution initially showed the presence of SOCl$_2$, but, after several hours, a POC$^+$H$_3$ doublet appeared and the SOCl$_2$ peak decreased in intensity. A solid precipitated, identified as 3-(trimethylammonium)propane sulfobetaine. Methyl isopropyl methylphosphonate was isolated; the infrared and nmr spectra of the compound in carbon tetrachloride were identical with those of an authentic sample. The nmr spectrum con-
tained a POC$^+$H$_3$ multiplet centered at 8 5.35 (one proton), and a POC$^+$H$_3$ doublet at 8 6.36 ($J$ 11 cps). A POC$^+$H$_3$ doublet occurred at 8 6.86 ($J$ 18 cps), and a CCH$_2$ doublet (two methyls, six protons) appeared at 8 8.71 ($J$ 6 cps). This experiment was repeated in deuterium oxide at a concentration of substrate of ca. 0.3%. Although solvolysis predominated, the POC$^+$H$_3$ peak was observed; methyl isopropyl methylphosphonate was isolated and confirmed by an nmr spectrum (CCL$_3$). A control study showed that isopropyl methylphosphonic acid was not esterified by methanol.

Registry No.—1-Methyl-3-(methylsulfonyl)pyridinium perchlorate, 21876-83-5.
A series of 18 new, water-soluble alkylating agents was synthesized. The structures contain an alkylsulfonate group as the alkylating function and a quaternary ammonium salt group attached to a hydrocarbon backbone. Alkylation rate data were obtained for 16 anion nucleophiles in aqueous media at 25^oC (and 37^oC) and constant salt concentration using 1-methyl-3-(methylsulfonate)pyridinium perchlorate as the alkylating agent substrate. The data at 25^oC are presented in terms of log k_2/k_w and the Swain and Scott equation is employed to obtain the substrate constant, s (0.715). Nucleophilic constants, n, are calculated and compared with published values for 12 anions, and new constants were determined for four phosphonate ion species.