AD 706905

AD

EDGEWOOD ARSENAL
SPECIAL PUBLICATION
EASP 100-74

I. ALKYLATING AGENTS CONTAINING A QUATERNARY NITROGEN GROUP

II. RELATIVE NUCLEOPHILICITY. METHYLATION OF ANIONS IN AQUEOUS MEDIA

by

Joseph Epstein
Harry O. Michel
Defensive Research Department
Physical Research Laboratory

Brennie E. Hackley, Jr.
Physiology Department
Medical Research Laboratory

and

A. B. Ash
P. Blumbergs
C. L. Stevens
F. A. Daniher
Ash Stevens Inc.

June 1970

DEPARTMENT OF THE ARMY
EDGEWOOD ARSENAL
Research Laboratories
Physical Research Laboratory
Medical Research Laboratory
Edgewood Arsenal, Maryland 21010

DDC
RECEIVED
JUL 1 1970
C

EDGEWOOD ARSENAL SPECIAL PUBLICATION

EASP 100-74

I. ALKYLATING AGENTS CONTAINING A QUATERNARY NITROGEN GROUP
II. RELATIVE NUCLEOPHILICITY. METHYLATION OF ANIONS IN AQUEOUS MEDIA

by

Joseph Epstein
Harry O. Michel

Defensive Research Department
Physical Research Laboratory

Brennie E. Hackley, Jr.

Physiology Department
Medical Research Laboratory

and

A. B. Ash
P. Blumbergs
C. L. Stevens
F. A. Daniher

Ash Stevens Inc.

June 1970

This document has been approved for public release and sale; its distribution is unlimited.

Task 1A012501B02802

DEPARTMENT OF THE ARMY
EDGEWOOD ARSENAL
Research Laboratories
Physical Research Laboratory
Medical Research Laboratory
Edgewood Arsenal, Maryland 21010

FOREWORD

The work described in this report was authorized under Task 1AC12501B02802, Life Sciences Basic Research in Support of Materiel, Chemical.

This report (two articles) is reprinted from the Journal of Organic Chemistry 34, 4065-4072 (1969). Copyright 1969 by the American Chemical Society and reprinted by permission of the copyright owner. Letter of permission to use this copyright material is on file in the Office of Counsel, Edgewood Arsenal, Edgewood, Maryland 21010. Reproduction of the copyrighted material in whole or in part is prohibited except with permission of the copyright owner; however, Defense Documentation Center and the Clearinghouse for Federal Scientific and Technical Information are authorized to reproduce the document.

[Reprinted from the Journal of Organic Chemistry, 34, 4065 (1969).]
Copyright 1969 by the American Chemical Society and reprinted by permission of the copyright owner.

Alkylating Agents Containing a Quaternary Nitrogen Group[1]

P. Blumbergs, A. B. Ash, F. A. Daniher, C. L. Stevens,

Ash Stevens Inc., Detroit, Michigan 48202

H. O. Michel, B. E. Hackley, Jr., and J. Epstein

Research Laboratories, Edgewood Arsenal, Edgewood Arsenal, Maryland 21010

Received June 27, 1969

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.

A large body of literature exists on the blocking or inhibition of the enzyme acetylcholinesterase by various phosphorus poisons.[2] Thus, alkyl methylphosphonofluoridates become attached to the enzyme site, presumably by phosphonylation of an O-serine component of the enzyme protein.[3] The result is that the normal enzyme function of hydrolyzing acetylcholine is prevented. Removal of the phosphonate 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 anion.[4] The net result is

(1) This work was performed under Edgewood Arsenal Contract DA 18-108-AMC-262(A).

(2) "Handbuch der Experimentellen Pharmakologie," Vol XV, G. B. Koelle, Subeditor, "Cholinesterases and Anticholinesterase Agents," 1963, and/or R. D. O'Brien, "Toxic Phosphorus Esters," Academic Press, New York, N. Y., 1960.

(3) N. K. Schaffer, S. C. May, Jr., and W. H. Summerson, *J. Biol. Chem.*, **202**, 67 (1953).

(4) F. Berends, C. H. Posthumus, I. V. D. Sluys, and F. A. Deserkauf, *Biochim. Biophys. Acta*, **36**, 576 (1959).

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 alkylating 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 pK_a values approximately 2).[5] Accordingly, a highly reactive alkylating agent was required and an ester of a stronger acid was a likely choice. 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

$$(CH_3)_3N^+(CH_2)_nSO_3CH_3 \cdot X^-$$

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 alkylating 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.[6]

Results and Discussion

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

Inasmuch as 3-(trimethylammonium)propane sulfobetaine was rapidly prepared from the commercially available 3-hydroxypropanesulfonic acid sultone by ring opening with trimethylamine, attempts were made to convert the sulfobetaine to the sulfonyl chloride with phosphorus pentachloride and chlorosulfonic acid, or with thionyl chloride and catalytic quantities of dimethylformamide.[7] Formation of crude sulfonyl 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 (185–193°) for 3 hr to yield a crude methyl sulfate 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.

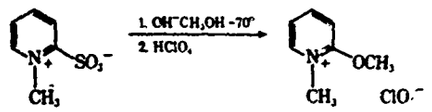
$$(CH_3)_3N^+(CH_2)_3SO_3^- + (CH_3O)_2SO_2 \xrightarrow{185°}$$

$$(CH_3)_3N^+(CH_2)_3SO_3CH_3 \cdot CH_3OSO_3^- \xrightarrow[2.\ HClO_4]{1.\ \text{Dowex-1 } (OH^-)/-70°}$$

$$(CH_3)N^+(CH_2)_3SO_3CH_3 \cdot ClO_4^-$$

The method proved general and was applied to all alkylating 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[1] 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 6–16%, 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 sulfate. However, all attempts to prepare 2- and 4-(methylsulfonate)-1-methylpyridinium perchlorate failed. Interestingly, it was discovered that both the 2- and 4-pyridinium sulfobetaines were converted to the 2- and 4-methoxy-1-methylpyridinium perchlorate by passage in 70% methanol–water (v/v) over the Dowex-1 (hydroxide) column and neutralization of the effluent with perchloric acid.



The precursor sulfobetaines are stable, high-melting (230–367°), neutral, and water-soluble inner salts, insoluble in organic solvents. They were prepared by (a) treatment of ω-haloalkylsulfonic acids or their salts with tertiary amines; (b) treatment of ω-tertiary amine alkyl halides with sodium sulfite; or (c) ring opening of the corresponding cyclic sultones with tertiary amines. The alkylating agents are solubie in polar solvents such as water, acetone, and acetonitrile and slightly soluble in methanol. All new compounds were characterized by elemental analysis, infrared spectra, and, in selected cases, nmr spectra. The alkylating agents are listed in Table I with melting point and yield data.

Experimental Section

Compound 3–18 were prepared from the precursor sulfobetaine, generally *via* the cyclic sultone. 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-(ethylsulfonate)-1-ethylpyridinium perchlorate (2) were prepared directly from 3-pyridinesulfonic acid and dialkyl sulfate.

(5) A. G. Ogston, E. R. Holiday, J. St. L. Philpot, and L. A. Stocken, *Trans. Faraday Soc.*, **44**, 45 (1948).

(6) A. B. Ash, P. Blumbergs, C. L. Stevens, H. O. Michel, B. E. Hackley, Jr., and J. Epstein, *J. Org. Chem.*, **34**, 4070 (1969).

(7) H. H. Bosshard, *et al.*, *Helv. Chim. Acta*, **42**, 1653 (1959).

TABLE I

ALKYLATING AGENTS

Compd	Structure (perchlorate salt)	Mp, °C	Yield, %[a]
1	CH_3-pyr-3-SO_3CH_3	113.5–115	20[b]
2	C_2H_5-pyr-3-$SO_3C_2H_5$	94.5–96.5	30[b]
3	$(CH_3)_3N^+(CH_2)_3SO_3CH_3$	145–146.5	45
4	$(CH_3)_3N^+(CH_2)_3SO_3CH_3$	116–118	80
5	$(C_2H_5)_3N^+(CH_2)_3SO_3CH_3$	86–88	53
6	$C_5H_5N^+(CH_2)_3SO_3CH_3$	118–120	70
7	$(CH_3)_3N^+(CH_2)_3SO_3C_2H_5$	95.5–96.5	65
8	$(CH_3)_3N^+CH(CH_3)CH_2C(CH_3)_2SO_3CH_3$	117–119	60
9	$C_5H_5N^+CH(CH_3)CH_2C(CH_3)_2SO_3CH_3$	93–94	75
10	$(CH_3)_3N^+(CH_2)_4SO_3CH_3$	91–93	74
11	$(C_2H_5)_3N^+(CH_2)_4SO_3CH_3$	74–77	80
12	$C_5H_5N^+(CH_2)_4SO_3CH_3$	86–87	65
13	$(CH_3)_3N^+CH(C_2H_5)(CH_2)_3SO_3CH_3$	115–119	63
14	$C_5H_5N^+CH(C_2H_5)(CH_2)_3SO_3CH_3$	81–83	77
15	$(CH_3)_3N^+(CH_2)_5SO_3CH_3$	74–76	78
16	$(CH_3)_3N^+(CH_2)_6N^+(CH_3)_2(CH_2)_5SO_3CH_3$	181–182	70
17	$[CH_3O_3S(CH_2)_3N^+(CH_3)_2(CH_2)_2]_2$	153–155	32
18	$CH_3O_3S^-(CH_2)_3N^+(CH_3)_2(CH_2)_3SO_3CH_3$	105–106.5	28[c]

[a] From precursor sultobetaine and dialkyl sulfate unless otherwise indicated. [b] From 3-pyridinesulfonic acid and dialkyl sulfate. [c] From the precursor sulfonic acid and dimethyl sulfate.

All melting points are uncorrected. 3-Hydroxypropanesulfonic acid sultone and 3-hydroxy-1,1,3-trimethylpropanesulfonic acid sultone were obtained from the Shell Chemical Corp.

General Procedure. Methyl 3-(Trimethylammonium Perchlorate)propane Sulfonate (4).—3-Hydroxy-1-propanesulfonic acid sultone (61 g) was added to trimethylamine (30 g) in benzene with stirring. The heat of reaction maintained the temperature at 35–40°. The mixture was warmed to 50–60° for 1 hr and allowed to stand overnight at room temperature. The mixture was filtered and the wet solid was stirred and heated with ethanol (300 ml). The cooled mixture was filtered to isolate crude 3-(trimethylammonium)propane sulfobetaine, 84 g (82%), mp 344–346° dec with darkening at 330°. An additional 7 g of product was recovered from the mother liquor. The product was recrystallized from methanol to give mp 347–349° dec, the melting point varies with the rate of heating.

Anal. Calcd for $C_6H_{15}NO_3S$: C, 39.76; H, 8.34; S, 17.69. Found: C, 39.55; H, 8.45; S, 17.49.

The sulfobetaine (1.8 g) was refluxed in dimethyl sulfate (10 ml) for 2 hr, cooled, and leached with dry ether. The residue was dissolved in cold methanol and passed over a methanolic Dowex-1-X2 (hydroxide form) ion-exchange resin column cooled at −70°. The eluate was immediately neutralized with 70% perchloric acid. The crystalline precipitate was filtered, washed with cold methanol, and recrystallized from acetone–ether (or acetone–methanol–ether) to yield 2.38 g (80%) of compound 4, mp 116–118°. The nmr spectrum was compatible with the assigned structure.

Anal. Calcd for $C_7H_{18}ClNO_7S$: C, 28.43; H, 6.13; N, 4.74; S, 10.84. Found: C, 28.48; H, 6.15; N, 4.56; S, 10.59.

Methyl 3-(triethylammonium perchlorate)propane Sulfonate (5).—Triethylamine and 3-hydroxy-1-propanesulfonic acid sultone in benzene solution at room temperature gave 33% crude product. Two recrystallizations from ethanol–acetone–ether gave an analytical sample, mp 296–298° dec, of 3-(triethylammonium)propane sulfobetaine.

Anal. Calcd for $C_9H_{21}NO_3S$: C, 48.40; H, 9.48; S, 14.36. Found: C, 48.25; H, 9.73; S, 14.24.

The sulfobetaine was treated with dimethyl sulfate, according to the standard procedure, to give compound 5 (53%), mp 86–88°, after recrystallization from acetone–methanol–ether.

Anal. Calcd for $C_{10}H_{24}ClNO_7S$: C, 35.55; H, 7.16; Cl, 10.50; N, 4.15; S, 9.49. Found: C, 35.75; H, 7.10; Cl, 10.55; N, 4.22; S, 9.48.

Methyl 3-(Pyridinium perchlorate)propane Sulfonate (6).—Pyridine and the propane sultone in acetone solution at room temperature gave 3-(pyridinium)propane sulfobetaine (75%), mp 273–275° dec, from methanol–ether.

Anal. Calcd for $C_8H_{11}NO_3S$: C, 47.74; H, 5.51; N, 6.96; S, 15.93. Found: C, 47.60; H, 5.50; N, 7.01; S, 16.14.

The sulfobetaine was treated with dimethyl sulfate by the standard procedure to give crude title compound, mp 117–119°. Recrystallization from acetone–ether gave an analytical sample, mp 118–120°.

Anal. Calcd for $C_9H_{14}ClNO_7S$: C, 34.23; H, 4.47; N, 4.43; S, 10.15. Found: C, 34.37; H, 4.36; N, 4.39; S, 9.90.

Ethyl 3-(Trimethylammonium perchlorate)propane Sulfonate (7).—The yield of product from the precursor, 3-(trimethylammonium)propane sulfobetaine, was 65%, mp 94–96°. An analytical sample from acetone–ether had mp 95.5–96.5°.

Anal. Calcd for $C_8H_{18}ClNO_7S$: C, 31.02; H, 6.50; N, 4.52; S, 10.35. Found: C, 31.33; H, 6.48; N, 4.53; S, 10.37.

Methyl 3-(Trimethylammonium perchlorate)-1,1,3-trimethylpropane Sulfonate (8).—3-Hydroxy-1,1,3-trimethylpropanesulfonic acid sultone was placed in a sealed tube with trimethylamine for 4 days to yield crude 3-(trimethylammonium)-1,1,3-trimethylpropane sulfobetaine (33%), mp 256–258° dec. Recrystallization from methanol–ether gave an analytical sample, mp 260° dec.

Anal. Calcd for $C_9H_{21}NO_3S$: C, 48.39; H, 9.48; N, 6.28; S, 14.35. Found: C, 48.25; H, 9.45; N, 6.45; S, 14.38.

The sulfobetaine was heated with excess dimethyl sulfate for 6 hr at 115–125° to give the title compound (60%), mp 117–118°. Recrystallization from acetone–ether gave an analytical sample, mp 117–119°.

Anal. Calcd for $C_{10}H_{24}ClNO_7S$: C, 35.55; H, 7.16; N, 4.14; S, 9.49. Found: C, 35.46; H, 7.40; N, 3.87; S, 9.65.

Methyl 3-(Pyridinium perchlorate)-1,1,3-trimethylpropane Sulfonate (9).—3-Hydroxy-1,1,3-trimethylpropanesulfonic acid sultone was heated in excess pyridine at 90° for 3 hr to yield crude 3-(pyridinium)-1,1,3-trimethylpropane sulfobetaine (62%), mp 251–253° dec. Recrystallization from methanol–ether gave an analytical sample, mp 254–255° dec.

Anal. Calcd for $C_{11}H_{17}NO_3S$: C, 54.29; H, 7.04; N, 5.76; S, 13.18. Found: C, 54.17; H, 7.09; N, 5.79; S, 13.42.

The sulfobetaine was converted to the methyl ester by the standard procedure in 75% yield, mp 90–92°, from acetone–ether.

Anal. Calcd for $C_{12}H_{26}ClNO_7S$: C, 40.28; H, 5.63; N, 3.91; S, 8.99. Found: C, 40.48; H, 5.84; N, 3.96; S, 9.02.

Methyl 4-(Trimethylammonium perchlorate)butane Sulfonate (10).—Butane sultone was prepared from tetrahydrofuran *via* 4-chlorobutyl acetate and 4-hydroxybutylsulfonic acid by the method of Helberger.[8] The sultone was treated with a 50% excess of trimethylamine in benzene (gentle reflux). The system was sealed and refluxed for 3 days. Work-up gave 3-(trimethylammonium)butane sulfobetaine (75%), mp 354° dec (lit.[9] mp 300°), from water–ethanol–ether.

Anal. Calcd for $C_7H_{17}NO_3S$: C, 43.05; H, 8.78; S, 16.42. Found: C, 42.58; H, 9.06; S, 16.12.

The sulfobetaine was converted to the title compound (74%), mp 90–92°. Recrystallization from acetone–methanol–ether gave mp 91–93°.

Anal. Calcd for $C_8H_{19}ClNO_7S$: C, 31.02; H, 6.51; N, 4.52; S, 10.35. Found: C, 31.16; H, 6.53; N, 4.29; S, 10.38.

Methyl 4-(Triethylammonium perchlorate)butane Sulfonate (11).—Butane sultone (1 mol) and triethylamine (3 mol) were stirred for 4 days and allowed to stand for 7 days at room temperature. Excess amine was decanted. The solid was washed with ether, dissolved in methanol, and passed over a Dowex-1-X2 (hydroxide) column. 4-(Triethylammonium)butanesulfobetaine (52%), mp 296–298° dec, was isolated from the eluate. Recrystallization from ethanol–ether–acetone gave mp 298–299° (lit.[9] mp 279°).

Anal. Calcd for $C_{10}H_{23}NO_3S$: C, 50.60; H, 9.77; S, 13.51. Found: C, 50.30; H, 9.84; S, 13.84.

The sulfobetaine was converted to the title compound (80%) by the standard procedure; it had mp 74–77° after recrystallization from warm methanol containing a trace of acetone.

Anal. Calcd for $C_{11}H_{26}ClNO_7S$: C, 37.55; H, 7.45; Cl, 10.08; S, 9.11. Found: C, 37.81; H, 7.46; Cl, 10.26; S, 8.95.

Methyl 4-(Pyridinium perchlorate)butane Sulfonate (12).—Butane sultone was heated in pyridine for 3 hr (steam bath). Work-up gave a 52% yield of crude 4-(pyridinium)butane sulfobetaine, mp 229–231° dec. Recrystallization from methanol–ether gave mp 231° dec (foaming).

(8) J. H. Helberger and H. Lantermann, *Ann.*, **588**, 160 (1954).
(9) B. Helferich, *ibid.*, **667**, 37 (1961).

Anal. Calcd for $C_9H_{13}NO_3S$: C, 50.17; H, 6.08; N, 6.51; S, 14.89. Found: C, 50.21; H, 6.13; N, 6.51; S, 15.09.

The sulfobetaine was converted to the title compound (65%), mp 84–86°. Recrystallization from acetone–ether gave an analytical sample, mp 86–87°.

Anal. Calcd for $C_{10}H_{16}ClNO_3S$: C, 36.41; H, 4.88; N, 4.24; S, 9.72. Found: C, 36.66; H, 5.02; N, 4.22; S, 9.89.

Methyl 4-Ethyl-4-(trimethylammonium perchlorate)butane Sulfonate (13).—6-Hydroxyhexanesulfonic acid, prepared from 1-acetoxy-6-chlorohexane by treatment with aqueous sodium sulfite, was cyclized at 155° at 1-mm pressure to yield 4-ethylbutane sultone, bp 102–105° (1.0 mm), according to the method of Helferich.[10] The overall yield from 1-acetoxy-6-chlorohexane was 32%. 4-Ethylbutane sultone was heated with trimethylamine in a sealed tube at 110° for 12 hr. The hygroscopic product, 4-ethyl-4-(trimethylammonium)butane sulfobetaine (15%), after recrystallization from ethanol–ether, had mp 238–240°. The sulfobetaine was converted to the title compound (63%). After recrystallization from acetone–ether, the product had mp 115–118°.

Anal. Calcd for $C_{10}H_{22}ClNO_3S$: C, 35.54; H, 7.16; N, 4.17; S, 9.46. Found: C, 35.56; H, 6.99; N, 4.42; S, 9.16.

Methyl 4-Ethyl-4-(pyridinium perchlorate)butane Sulfonate (14).—4-Ethylbutane sultone, prepared as above, was refluxed in excess pyridine for 2 days to give 4-ethyl-4-(pyridinium)butane sulfobetaine (72%), mp 253–255°, after recrystallization from methanol–ether. The sulfobetaine was converted to the title compound (77%), mp 81–83°, after recrystallization from acetone–ether.

Anal. Calcd for $C_{11}H_{16}ClNO_3S$: C, 40.28; H, 5.63; N, 3.91. Found: C, 40.43; H, 5.71; N, 4.04.

Methyl 6-(Trimethylammonium perchlorate)hexane Sulfonate (15).—Hexamethylene chlorohydrin (50 g) and trimethylamine (35 g) were dissolved in benzene and allowed to stand for 60 hr. Filtration yielded crude 6-hydroxyhexyl trimethylammonium chloride (13 g, 0.068 mol) and starting material (41 g). The crude product (10 g) was dissolved in thionyl chloride (20 ml). After standing overnight, the solution was refluxed for 2 hr, thionyl chloride was removed, and methanol was added. The solution was concentrated, diluted with benzene–methanol, and decolorized. Removal of solvents gave a gum which turned to mushy crystals under benzene. The dried crystals titrated as 30.5% ionic chloride *vs.* the theoretical 33.1% and were used directly in the next step. The crude product was dissolved in water (60 ml) containing sodium sulfite (6.24 g) and the solution was heated at 100° for 8 hr. The solution was concentrated, diluted with ethanol, and concentrated. The solid residue was extracted with ethanol (80 ml), decolorized, and diluted with acetone. After the residue cooled, 5.5 g of solid, mp 354–356° dec, was obtained. The mother liquor yielded additional product (1.7 g). The combined solids were dissolved in methanol and passed over Dowex-1-X2 (hydroxide) and Dowex-50 (acid) columns. Crystallization from ethanol–acetone gave 4.3 g (38%) of 6-(trimethylammonium)hexane sulfobetaine, mp 367° dec, based on chlorohydrin reacted. The sulfobetaine (2.23 g) was refluxed with dimethyl sulfate (10 ml) and worked up in the usual manner. The product isolated from the Dowex-1-X2 (hydroxide) column effluent was recrystallized from acetone–methanol–ether to give the title compound (2.65 g, 78%), mp 74–76°.

Anal. Calcd for $C_9H_{22}ClNO_3S$: C, 35.55; H, 7.16; S, 9.49. Found: C, 35.41; H, 7.25; S, 9.44.

3-(Methylsulfonate)-1-methylpyridinium Perchlorate (1). A. Dowex Method.—3-Pyridinesulfonic acid (200 mg) was heated with dimethyl sulfate (2 ml) for 3 hr (oil bath) at 180°. The mixture was triturated with ether. The residual gummy solid, poorly soluble in methanol, was dissolved in a minimum volume of ice–water and the solution was diluted to *ca.* 70% (v/v) with methanol. The solution was passed over a Dowex-1-X2 (hydroxide) ion-exchange column at −70° and the eluate was immediately neutralized with perchloric acid. The eluate was concentrated cold to a small volume and diluted with ether. The precipitated solid was collected and triturated with acetone. Acetone was removed from the extract and the solid was recrystallized from acetone–ether to yield the title compound (60 mg, 16%), mp 114–115° with previous softening. Recrystallization gave an analytical sample, mp 113.5–115°.

Anal. Calcd for $C_7H_{10}ClNO_7S$: C, 29.22; H, 3.50; N, 4.87; S, 11.15. Found: C, 29.13; H, 3.52; N, 5.31; S, 10.99.

(10) B. Helferich and V. Boellert, *Chem. Ber.*, **94**, 505 (1961).

The nmr spectrum was compatible with the assigned structure. The acetone-insoluble portion was recrystallized to yield 1-methyl-3-pyridinium sulfobetaine (100 mg, 46%), mp 351–353°. The sulfobetaine was prepared also directly by treating 3-pyridinesulfonic acid with a tenfold weight excess of dimethyl sulfate at 160–170° for 20 hr. The solid product which separated was recrystallized twice from water–methanol to yield 85% product, mp 355–358° dec.

Anal. Calcd for $C_6H_7NO_3S$: C, 41.61; H, 4.07; N, 8.09. Found: C, 41.77; H, 4.33; N, 8.19.

Treatment of 1-methyl-3-pyridinium sulfobetaine with dimethyl sulfate in the same manner as with 3-pyridinesulfonic acid gave only a 4% yield of compound 1.

B. Barium Perchlorate Method.—Extensive studies led to the following optimum procedure. 3-Pyridinesulfonic acid (1 g) was heated for 6 hr with dimethyl sulfate (10 ml) at 180°, or slightly below reflux. Excess dimethyl sulfate was removed by extraction with anhydrous ether. The syrupy residue was dissolved in 25 ml of acetone/g of sulfonic acid. A filtered solution of barium perchlorate in acetone, about 65 g/l. (prepared separately), was then added to the extent of 0.35 mol/mol of sulfonic acid to the acetone solution of reaction product. A little decolorizing carbon was added and the mixture was filtered (Filter Aid). Anhydrous ether was slowly added to the filtrate with swirling to a slight turbidity. When precipitation was complete, the mixture was cooled to 5° with further additions of ether as necessary. About two volumes of ether per volume of acetone are required. The crude ester was filtered and washed with dry ether to give product with mp 111–113°. The product was recrystallized once to give mp 114–115°; recovery was about 90%. The overall yield of recrystallized product was about 20% based on 3-pyridinesulfonic acid.

3-(Ethylsulfonate)-1-ethylpyridinium Perchlorate (2).—3-Pyridinesulfonic acid (5 g) and diethyl sulfate (100 ml) were heated rapidly to reflux (200–210°) under a nitrogen atmosphere. The mixture was held at reflux for not more than 10 min and cooled. The reaction mixture was leached with ether and the residue was dissolved in methanol. The methanolic solution was passed over a Dowex-1-X2 (hydroxide) ion-exchange resin column at −70°. The eluate was passed directly into 100 ml of ether containing 2 ml of perchloric acid also cooled to −70°. More ether was added until precipitation was complete. The product was filtered, washed with ether, and recrystallized from acetone–ether to yield 2.8 g (30%) of the ethyl ester 2, mp 94.5–96.5°.

Anal. Calcd for $C_9H_{14}ClNO_7S$: C, 34.29; H, 4.44; N, 4.44; S, 10.16. Found: C, 34.38; H, 4.60; N, 4.42; S, 10.18.

Methyl 2-(Trimethylammonium perchlorate)ethane Sulfonate (3).—Sodium 2-bromoethane sulfonate[11] was dissolved in excess 25% aqueous trimethylamine and allowed to stand for 10 days. The solution was concentrated to near dryness, diluted with absolute ethanol, and filtered. The solid was triturated with hydrochloric acid and filtered and the filtrate was concentrated to a thick syrup. Methanol and 2-propanol were added and the resulting solid was collected. The solid was dissolved in water and passed through a column of Dowex-50-X2 in water. The solution was again concentrated to near dryness. Absolute ethanol was added and the resulting solid was collected. The product was recrystallized from ethanol–water to yield trimethyl taurine (66%), mp 344–346°.

Trimethyl taurine was also prepared in 89% yield from ethylene bromide by the method of Barnhurst.[12] Trimethyl taurine (0.84 g) was refluxed with dimethyl sulfate (5 ml) for 1 hr. After the mixture was leached with ether, the slightly gummy solid was dissolved in methanol, decolorized, and passed over two Dowex-1-X2 (perchlorate form) resin columns (1.3 × 40 cm). The solution was concentrated in the cold. The resulting solid was filtered and crystallized twice from acetone–ether to yield compound 3, 0.32 g (23%), mp 146–147°. In an improved procedure, the solid from the dimethyl sulfate reaction was washed with a small volume of ice-cold methanol, dissolved in methanol, and treated with a methanol solution of anhydrous barium perchlorate at room temperature. The reaction mixture was cooled to 0° and filtered, and the solid crude product was washed with cold methanol. After recrystallization from acetone–ether, the product had mp 145–146.5°. The overall yield by this procedure is 40–50%.

(11) C. S. Marvel and M. S. Sparberg, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 558.

(12) J. D. Barnhurst, *J. Org. Chem.*, **26**, 4520 (1961).

Anal. Calcd for $C_6H_{10}ClNO_3S$: C, 25.58; H, 5.73; Cl, 12.58; N, 4.97; S, 11.38. Found: C, 25.84; H, 5.76; Cl, 12.54; N, 4.96; S, 11.20.

Attempted Preparation of 2- and 4-(Methylsulfonate)-1-methylpyridinium Perchlorates.—2-Bromopyridine was converted to 2-mercaptopyridine in 85% yield, yellow needles, mp 120–124° (crude), following the method of Thirtle.[13] The mercaptan was then oxidized with nitric acid to 2-pyridinesulfonic acid (67%), mp 246–247.5°, by the method of Evans and Brown,[14] who report mp 251–252°.

To prepare 4-pyridinesulfonic acid, pyridine was treated with thionyl chloride (initial cooling required) for 5 days and worked up according to the method of Bowden and Green.[15] In our hands, the yield was 16% crude material, mp 100–150°. The crude material was converted to 4-pyridinesulfonic acid by treatment with sodium sulfite according to the method of Evans and Brown[14] and gave, after purification by ion exchange, *ca.* 30% 4-pyridinesulfonic acid, mp 325–328° dec (lit.[14] mp 317–318°).

As discussed in the text, the reaction of both 2- and 4-pyridinesulfonic acid with dimethyl sulfate and work-up in the usual manner (Dowex-1 (hydroxide) column technique) gave a sulfur-free product corresponding to the 1-methyl-2- (and 4-) methoxypyridinium perchlorates. Further study indicated that the dimethyl sulfate reaction forms the corresponding 2- and 4-pyridine sulfobetaines (no methyl esters were isolated), which are readily displaced by methoxide on the Dowex-1 (hydroxide) column even at *ca.* −70°.

In a typical experiment, purified 2-pyridinesulfonic acid (1.0 g) was treated with dimethyl sulfate (10 ml) at 140° for 3 hr. After the mixture was leached with ether, the residue was dissolved in 70% methanol–water (v/v) and passed over a Dowex-1-X2 (hydroxide) column at −70°. The eluate was immediately neutralized with perchloric acid, diluted three times with ether, and cooled in Dry Ice–acetone to yield crude product (980 mg, 60%). Recrystallization from acetone–ether gave 850 mg of 2-methoxy-1-methylpyridinium perchlorate, mp 114–116°.

Anal. Calcd for $C_7H_{10}ClNO_6$: C, 37.60; H, 4.51; N, 6.26. Found: C, 37.93; H, 4.56; N, 6.29.

To gain more information, 1-methyl-2-pyridinium sulfobetaine was prepared by treating 2-pyridinesulfonic acid with dimethyl sulfate at 140° for 3 hr. The reaction mass was worked up as for 1-methyl-3-pyridinium sulfobetaine (see above) and gave 58% product, mp 268° dec.

Anal. Calcd for $C_6H_7NO_3S$: C, 41.61; H, 4.07; N, 8.09; S, 18.51. Found: C, 41.84; H, 4.17; N, 7.80; S, 18.16.

The sulfobetaine (110 mg) was dissolved in 70% methanol–water (v/v) and passed over a Dowex-1-X2 (hydroxide) ion-exchange column at −70°. The eluate was neutralized at once with perchloric acid. There was isolated 2-methoxy-1-methylpyridinium perchlorate (105 mg, 74%), mp 113–115°. A mixture melting point with the original analytical sample was undepressed and the infrared spectra were identical. The perchlorate salt was converted to crude bisulfate salt by ion exchange: mp 115–130°; bisulfate absorption in the infrared spectrum at 8.6, 9.86, and 11.65 μ. An attempt to prepare the chloride salt gave an oil.

Similar results were observed in the reaction of 4-pyridinesulfonic acid with excess dimethyl sulfate at 145° for 4 hr. Work-up in the usual manner and passage over a Dowex-1-X2 (hydroxide) column gave a yellow solid, 4-methoxy-1-methylpyridinium perchlorate (100 mg), mp 68–72°. Recrystallization from acetone–ether with decolorization gave an analytical sample, mp 72–74°, as near-white crystals. The infrared spectrum showed absorptions at 8.3 and 8.35 μ.

Anal. Calcd for $C_7H_{10}ClNO_6$: C, 37.60; H, 4.51; N, 6.26. Found: C, 38.05; H, 4.60; N, 6.31.

The product was unchanged on a second passage over the Dowex-1-X2 (hydroxide) column.

Preparation of Methyl 4-Aza-4,4-dimethyl-8-(trimethylammonium perchlorate)octyl Sulfonate Perchlorate (16).—Butylene diamine (9.8 g) was refluxed with aqueous formaldehyde (44 ml) and 90% formic acid (80 ml) for 35 hr. An equal volume of water containing concentrated hydrochloric acid (24 ml) was added and the mixture was evaporated to dryness. The solids were dissolved in minimum water which was made alkaline with 25% aqueous sodium hydroxide. The reaction mixture was extracted with ether. The extract was dried (potassium hydroxide) and the ether was removed. The resulting oil was distilled to yield a first-fraction (12.0 g), bp 155–163°, 95% pure by vpc, and a second fraction (2.9 g), bp 163–165°, 100% pure by vpc. The over-all yield was 90% of N,N,N′,N′-tetramethylbutylenediamine. Picrates of both fractions were prepared in 95% yield, mp 201–202° (lit.[16] mp 198–199°).

Methyl iodide (1.98 g, 14.4 mmol) in benzene (30 ml) was added dropwise to a stirred solution of the diamine (2.0 g, 14.4 mmol) in benzene (30 ml). The solution was stirred for 10 min and filtered. The precipitate was washed with benzene and dried to yield crude product (3.4 g), mp 141–143°. The latter was dissolved in ethanol and the presumed 1,4-diquaternary isomer (0.23 g) was removed by filtration. The filtrate was concentrated and the addition of ethyl acetate gave 4-(trimethylammonium iodide)-1-dimethylaminobutane (2.86 g, 70%), mp 146–147°.

Anal. Calcd for $C_9H_{23}IN_2$: C, 37.77; H, 8.10; I, 44.34; N, 9.79. Found: C, 37.73; H, 8.21; I, 44.48; N, 9.55.

4-(Trimethylammonium iodide)-1-dimethylaminobutane (2.0 g, 7.0 mmol) and propane sultone (0.85 g, 7.0 mmol) in benzene (50 ml) were refluxed for 4 hr. The mixture was filtered and the solid was recrystallized from methanol–acetone to give 1.65 g (60%) of 4-aza-4,4-dimethyl-8-(trimethylammonium iodide)octane sulfobetaine, mp 280–282°.

Anal. Calcd for $C_{12}H_{28}IN_2O_3S$: C, 35.29; H, 7.16; I, 31.08; N, 6.86; S, 7.85. Found: C, 35.34; H, 7.22; I, 31.29; N, 7.08; S, 7.91.

The sulfobetaine (1.12 g) was heated for 4 hr with dimethyl sulfate (5 ml). The mixture was triturated with ether and dissolved in methanol, and the solution was passed over Dowex-1 (hydroxide) at −70° into a cold solution of perchloric acid in methanol. The product was recrystallized from methanol–acetone–ether to give 1.0 g (70%) of the title compound **8**, mp 181–182°.

Anal. Calcd for $C_{13}H_{32}Cl_2N_2O_{11}S$: C, 31.52; H, 6.51; Cl, 14.31; N, 5.66; S, 6.47. Found: C, 31.81; H, 6.61; Cl, 14.20; N, 5.51; S, 6.42.

Preparation of Methyl 3,3′-Bis-(1,4-tetramethylammonium butane)propane Sulfonate Diperchlorate (17).—N,N,N′,N′-Tetramethylbutylenediamine (4.3 g, 0.030 mol) and propane sultone (7.4 g, 0.0605 mmol) were dissolved in benzene (60 ml) and the solution was refluxed overnight. The mixture was filtered and the precipitate was washed with benzene and dried. Crude 3,3′-bis(1,4-tetramethylammonium butane)propane sulfobetaine (11.0 g, 95%), mp 301–303° dec, was obtained. An analytical sample, mp 313–315° dec, was prepared by recrystallization twice from methanol–acetone.

Anal. Calcd for $C_{16}H_{32}N_2O_6S_2$: C, 43.27; H, 8.30. Found: C, 43.24; H, 8.05.

The disulfobetaine (3.9 g, 0.01 mol) was heated with dimethyl sulfate (25 ml) at 125–130° for 8 hr. Some material did not dissolve. After trituration with ether, the solid was dissolved in methanol and filtered to remove unreacted sulfobetaine and/or monoester. The methanol solution was passed over Dowex-1 (hydroxide) into methanol containing perchloric acid. The solid was filtered, washed with ether, and dried to give 2.5 g (40%) of crude compound **9**. A portion of the crude product was recrystallized twice from acetonitrile–ether to give mp 153–155°.

Anal. Calcd for $C_{18}H_{38}Cl_2N_2O_{16}S_2$: C, 31.11; H, 6.20; N, 4.54. Found: C, 31.60; H, 6.40; N, 4.69.

Preparation of Methyl 3,3′-Bis(dimethylammonium Perchlorate)propane Sulfonate (18).—Propane sultone (14.5 g, 0.12 mol) was let react with dimethylamine (6.0 g, 10% excess) in benzene solution. The solution was stirred at room temperature overnight and then refluxed for 1 hr. The precipitated betaine was filtered and washed with benzene to give, after one recrystallization from ethanol–acetone, 11.5 g (33%) of 3-dimethylammonium-N-(3′-sulfonopropyl)propane sulfobetaine, mp 215°, with previous softening at 204°, which (2.88 g, 0.1 mol) was heated with dimethyl sulfate (20 ml) at 115–120° for 16 hr. The reaction mixture was triturated with ether. The residual solid was dissolved in minimum methanol and passed through Dowex-1 (hydroxide) at −70°. The eluate was collected in methanol containing perchloric acid (2 ml). The product was filtered, washed with ether, and dried to give compound **10** (1.7 g, 40%), mp 97–98.5° after one recrystallization from acetonitrile–ether.

(13) J. R. Thirtle, *J. Amer. Chem. Soc.*, **68**, 342 (1946).
(14) R. C. Evans and H. C. Brown, *J. Org. Chem.*, **27**, 1327 (1962).
(15) K. Bowden and P. N. Green, *J. Chem. Soc.*, 1795 (1954).
(16) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Amer. Chem. Soc.*, **55**, 4571 (1933).

The product was purified further by trituration three times with boiling acetone. The acetone-soluble portion was filtered through Celite and ether was added to the filtrate. Compound 10 separated on slow cooling; mp 105–106.5°, 72% recovery.

Anal. Calcd for $C_{10}H_{24}Cl_2NO_3S$: C, 28.75; H, 5.79; N 3.35. Found: C, 29.01; H, 5.95; N, 3.45.

Registry No.—**1**, 21870-83-5; **2**, 21864-92-6; **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, 21865-17-8; 3-(triethylammonium)propane sulfobetaine, 1887-93-0; 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, 21876-42-6; 4-(pyridinium)-butane sulfobetaine, 21876-43-7; 4-ethyl-4-(trimethylammonium)butane sulfobetaine, 21876-44-8; 4-ethyl-4-(pyridinium)butane sulfobetaine, 21876-45-9; 6-(trimethylammonium)hexane sulfobetaine, 21876-46-0; 1-methyl-3-pyridinium sulfobetaine, 21876-47-1; trimethyl taurine, 7465-57-8; 2-methoxy-1-methylpyridinium perchlorate, 21876-49-3, 1-methyl-2-pyridinium sulfobetaine, 4329-93-5; 4-methoxy-1-methylpyridinium perchlorate, 21876-51-7; N,N,N′,N′-tetramethylbutylenediamine, 111-51-3; 4-(trimethylammonium-iodide)-1-dimethylaminobutane, 21876-53-9; 4-aza-4,4-dimethyl-8-trimethylammonium iodide octane sulfobetaine, 21876-54-0; 3,3′-bis(1,4-tetramethylammoniumbutane)propane sulfobetaine, 21876-55-1.

[Reprinted from the Journal of Organic Chemistry, 34, 4070 (1969).]
Copyright 1969 by the American Chemical Society and reprinted by permission of the copyright owner.

Relative Nucleophilicity. Methylation of Anions in Aqueous Media[1]

A. B. Ash, P. Blumbergs, C. L. Stevens,

Ash Stevens Inc., Detroit, Michigan 48202

H. O. Michel, B. E. Hackley, Jr., and J. Epstein

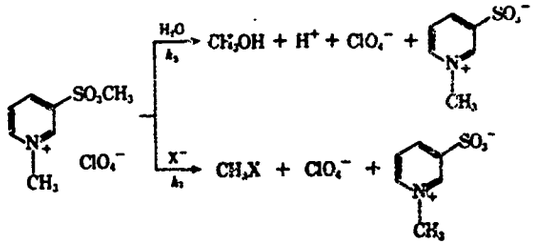
Research Laboratories, Edgewood Arsenal, Edgewood Arsenal, Maryland 21010

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_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.

The synthesis of a series of water-soluble alkylating agents has been described.[2] A pyridine analog, 1-methyl-3-(methylsulfonate)pyridinium perchlorate,[2] 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[3] method.

This alkylating agent, in common with other members of the series,[2] 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_s is the solvolysis rate constant and k_2 is the second-order anion alkylation rate constant.



The ratio of k_2/k_s and k_s 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 hydrolysis 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.

$$k_2/k_s = \frac{2.3 \log [S_0]/[S_t]}{[H^+_t]}$$

In this equation, $[S_0]$ is initial concentration of anion and $[S_t]$ is the concentration at time t, usually taken at infinity. The term $[H^+_t]$ 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_2/k_s 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_2/k_s are multiplied by 55.4, the molar concentration of water, to give k_2/k_w. A conventional Swain and Scott[3] treatment is based on the equation $\log k_2/k_s = sn$, where n is the anion nucleo-

(1) This work was performed under Edgewood Arsenal Contract DA 18-108-AMC-263(A).

(2) P. Blumbergs, A. B. Ash, F. A. Daniher, C. L. Stevens, H. O. Michel, B. E. Hackley, Jr., and J. Epstein, *J. Org. Chem.*, 34, 4065 (1969).

(3) C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.*, 75, 141 (1953).

TABLE I

RELATIVE NUCLEOPHILICITIES. SWAIN AND SCOTT METHOD[a]

[substrate: 1-methyl-3-(methylsulfonate)pyridinium perchlorate (25°, 0.1 *M* total salt, pH 7.0[c])]

Anion	k_2/k_s, M^{-1}	k_2/k_w	log k_2/k_w	Nucleophilic Constant *n* Obsd[b]	Lit.[c]
Nitrate	0.20	11	1.0	1.4	1.03
p-Nitrophenyl Methylphosphonate	0.27	15.0	1.18	1.7	...
Isopropyl Methylphosphonate	0.57	31.6	1.50	2.1	...
Fluoride	0.70	38.8	1.59	2.2	2.0
Sulfate	1.44	79.8	1.9	2.6	2.5
Chloride	2.61	145	2.16	3.02	3.04
Acetate	4.52	250	2.4	3.36	2.72
Chloromethylphosphonate (Dianion)	7.28	403	2.53	3.5	...
Bromide	10.9	604	2.78	3.89[d]	3.89
Bicarbonate	23	1300	3.1	4.3	3.8
Azide	27	1500	3.2	4.5	4.00
Thiocyanate	57.3	3170	3.5	4.89	4.77
Iodide	74.0	4100	3.61	5.05	5.04
Ethyl Methylthiophosphonate	150	8200	3.9	5.5	...
Hydroxide	480	26600	4.4	6.2	4.2
Thiosulfate	3500	190000	5.3	7.4	6.4

[a] Except acetate, 7.1; bicarbonate, 8.3; azide and chloromethylphosphonate, 9.0 (equivalence point). [b] Calculated from $s = 0.715$ (see footnote *d*). [c] All values from Swain and Scott,[3] except nitrate.[4] [d] Bromide ion taken as standard; $n = 3.89$.[3]

philic constant. A plot of log k_2/k_s *vs.* n is employed normally to determine the slope, s, the substrate constant.[3] In the present study, a plot of log k_2/k_s *vs.* the published nucleophilic constants[3] for chloride, bromide, and iodide ions was linear within 0.02 log units. Accordingly, bromide ion ($n = 3.89$)[3] 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 k_2/k_w by 0.715. The value of s of 0.715 for 1-methyl-3-(methylsulfonate)pyridinium perchlorate is comparable in magnitude with another sulfonate ester, ethyl *p*-toluenesulfonate (0.66).[3]

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

At 37°, with bromide ion as standard, the slope was 0.702, reflecting the decrease in k_2/k_s to 9.6 M^{-1} (from 10.9 M^{-1} at 25°). Nucleophilic constants for nine anions at 37° were in agreement with those observed at 25° within 0.1 log unit or less.

Experimental Section

A recording Sargent pH-Stat with thermoelectric temperature control (0.1°) was used. Solution volumes were 10–15 ml, 10^{-2}–10^{-3} *M* in agent, using 0.02–0.06 *N* sodium hydroxide as titrant with a nitrogen sweep. Sodium perchlorate was the added electrolyte to adjust the total salt concentration to 0.1 *M*. The infinity concentration of hydronium ion was adjusted for 60% of the volume of titrant. Five or more runs were made for each nucleophile in most cases and the results are reported to the number of significant figures 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 k_s was 9.18 ($\pm$0.10) $\times$ 10^{-6} sec^{-1}; at 37°, k_s is 3.07 ($\pm$0.12) $\times$ 10^{-5} sec^{-1}. The rate decreases with increasing salt concentration (see below).

Phosphonate and Thiophosphonate.—The alkylation of isopropyl methyl phosphonate was studied at 25°, 0.1 *M* in anion and 5 $\times$ 10^{-3} *M* in substrate. The ratio of k_2/k_s 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 k_2/k_s was 0.19 M^{-1}. 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*, 0.35. A comparative study of isopropyl methylphosphonate was made with five analogous agents at 37°, 0.70 *M* in phosphonate and 7 $\times$ 10^{-3} *M* in agent; the values of k_2/k_s ranged from 0.26 to 0.29, or constant within experimental error. To establish a nucleophilic constant for a phosphonate dianion, chloromethylphosphonic acid of high purity was used. The study was made at the equivalence point (pH 9.0), pK_{a_1} 2.14 and pK_{a_2} 6.41, as determined in water at 25°. In a system 0.5 *M* in dianion, the ratio of k_2/k_s at 25° was 5.20, corrected to 7.28 at 0.1 *M* salt concentration. The alkylation of ethyl methylthiophosphonate anion was studied at 25°, 1.72 $\times$ 10^{-3} *M* in substrate and 4.96 $\times$ 10^{-3} *M* in thiophosphonate adjusted to 0.1 *M* total salt with sodium perchlorate. The ratio k_2/k_s was 146 M^{-1}; at 37°, two runs gave the values 116 and 122 M^{-1}.

Other Anions.—Bromide ion, the standard, was studied at 37° over a range of total salt concentration. The observed values of k_2/k_s (M^{-1}), a function of total salt concentration (substrate plus bromide ion), are as follows: 0.026 *M*, 12.0; 0.088 *M*, 9.9; 0.100 *M*, 9.6; 0.26 *M*, 9.0; 0.30 *M*, 7.6; 0.50 *M*, 6.8; 0.71 *M*, 6.7. The corresponding values for k_s (sec^{-1}) $\times$ 10^5 are as follows: 0.026 *M*, 3.4; 0.088 *M*, 3.2; 0.100 *M*, 3.1; 0.126 *M*, 3.0; 0.30 *M*, 2.8; 0.71 *M*, 2.6. Alkylation of thiosulfate ion exceeded 90% even at a 1:1 mole ratio of substrate to the 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 mole ratios of bicarbonate to substrate; k_2/k_s values ranged from 21 to 26 M^{-1}, increasing (in this case) with increasing salt concentration. Azide ion was determined at pH 9.0 where the system appeared to be more stable than at pH 7.0. Thiocyanate ion was studied at pH 7.0 with good reproducibility. Chloride ion was checked independently using a sister agent, methyl 3-(trimethylammonium perchlorate)-sulfonate, 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^{-3} *M* in substrate. The results, k_2/k_s, were as follows (M^{-1}): nitrate, 0.17; *p*-nitrophenyl methylphosphonate, 0.19; isopropyl methylphosphonate, 0.41; fluoride, 0.51; sulfate, 1.02. Isopropyl methylphosphonate and sulfate ions were studied at a concentration of 0.1 *M* in anion plus agent to give k_2/k_s ratios of 0.57 and 1.44 M^{-1}. This corresponds, in both cases, to a factor of 1.4 in

(4) W. L. Petty and P. L. Nichols, Jr., *J. Amer. Chem. Soc.*, 76, 4385 (1954).

k_2/k_s between 0.5–0.1 M. This factor was used to estimate k_2/k_s at 0.1 M total salt for the other three less reactive anions (see bromide ion data above).

The ratios of k_2/k_s (M^{-1}), listed in Table I, were determined at 25°. At 37°, corresponding data (0.1 M total salt) for nine anions are as follows: isopropyl methylphosphonate, 2.0; fluoride, 2.1; chloride, 3.08; acetate, 3.42; bromide, 3.89 (standard); azide, 4.7; thiocyanate, 4.86; ethyl methylthiophosphonate, 5.5; iodide, 5.01.

Nmr Studies.—Nmr studies were made of the solvolysis of a sister agent, methyl 3-(trimethylammonium perchlorate)propane sulfonate,[3] in deuterium oxide, and the alkylation of sodium isopropyl methylphosphonate was studied in chloroform and dueterium oxide. All studies were carried out in an nmr tube using a Varian DP-60 operating at 60 Mcps. 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 $SOCH_3$ group at τ 6.1 and the appearance of the signal due to methanol at τ 6.6. 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 $SOCH_3$, but, after several hours, a $POCH_3$ doublet appeared and the $SOCH_3$ 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 contained a POCH multiplet centered at τ 5.35 (one proton), and a $POCH_3$ doublet at τ 6.36 (J = 11 cps). A PCH_3 doublet occurred at τ 8.66 (J = 18 cps), and a CCH_3 doublet (two methyls, six protons) appeared at τ 8.71 (J = 6 cps). This experiment was repeated in deuterium oxide at a concentration of substrate of *ca.* 20%. Although solvolysis predominated, the $POCH_3$ peak was observed; methyl isopropyl methylphosphonate was isolated and confirmed by an nmr spectrum (CCl_4). A control study showed that isopropyl methylphosphonic acid was not esterified by methanol.

Registry No.—1-Methyl-3-(methylsulfonato)pyridinium perchlorate, 21876-83-5.

UNCLASSIFIED

Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author)	2a. REPORT SECURITY CLASSIFICATION
CO, Edgewood Arsenal ATTN: SMUEA-RPR Edgewood Arsenal, Maryland 21010	UNCLASSIFIED
	2b. GROUP NA

3. REPORT TITLE

I. ALKYLATING AGENTS CONTAINING A QUATERNARY NITROGEN GROUP. II. RELATIVE NUCLEOPHILICITY. METHYLATION OF ANIONS IN AQUEOUS MEDIA

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)

5. AUTHOR(S) (First name, middle initial, last name)

Joseph Epstein, Harry O. Michel, Brennie E. Hackley, Jr., A. B Ash, P. Blumbergs, C. L. Stevens, and F. A. Daniher

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
June 1970	15	20

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
b. PROJECT NO.	EASP 100-74
c. Task No. 1A012501B02802	9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report) NA
d.	

10. DISTRIBUTION STATEMENT

This document has been approved for public release and sale; its distribution is unlimited.

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
Life sciences basic research in support of materiel, chemical	NA

13. ABSTRACT

(U) 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° (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_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.

14. KEYWORDS

Alkylating agents
Alkylation rates
Nucleophiles
Nucleophilic constants
Methylation
Solvolysis rate
1-Methyl-3-(methylsulfonate)pyridinium perchlorate
Isopropyl methylphosphonate
Ethyl methylthiophosphonate
p-Nitrophenyl methylphosphonate
Chloromethylphosphonate

DD FORM 1 NOV 68 1473 REPLACES DD FORM 1473, 1 JAN 64, WHICH IS OBSOLETE FOR ARMY USE.

UNCLASSIFIED

Security Classification