

The Synthesis and Reactions of β -Substituted Ethyl Sulfates

Donald A. Tomalia and John Carl Falk (1)

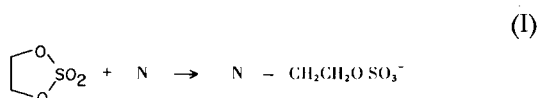
The Dow Chemical Company, E. C. Britton Research Laboratory,
Midland, Michigan 48640

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The synthesis of β -substituted ethyl sulfates and their reactions with nucleophilic reagents has been studied. Amines, phenolates, carboxylates, amine oxides, carbanions, and thiophenolates reacted with ethylene sulfate in high yield, with short reaction times, and at low temperatures, to form β -substituted ethyl sulfates. The β -substituted ethyl sulfates were easily hydrolyzed and in some cases were converted into polymeric material.

There has been considerable interest in recent years in the structure and reactivity of cyclic esters of sulfur (2-5). The high reactivity observed in the five membered cyclic esters has been attributed to the partial double bond character between the oxygen and sulfur atoms. This is a result of interaction between the oxygen (p)- and sulfur (d) orbitals. Recent x-ray studies reported by Boer, *et al.* (6), have shown a definite contraction in the sulfur-oxygen bond length of ethylene sulfate.

In a further study of the reactivity of cyclic five membered esters containing sulfur, this paper describes the synthesis of β -substituted ethyl sulfates by reacting ethylene sulfate with nucleophilic reagents, Reaction I.

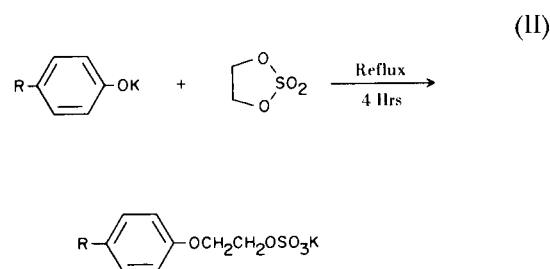


N = RNH₂, R-O⁻, R-CO₂⁻, R₃N-O, RS⁻ and R⁻

The nucleophilic displacement reactions which ethylene sulfate undergoes to form carbon-nitrogen, carbon-oxygen, carbon-sulfur, and carbon-carbon bonds are probably S_N2 in nature. The reactions of substituted anilines with ethylene sulfate to form β -anilino ethyl sulfate inner salts, Table I, are consistent with this interpretation. Aniline reacts rapidly with ethylene sulfate in refluxing methylene chloride, Entry 1, as do substituted anilines with electron releasing groups such as 4-methyl, Entry 2, and 4-methoxy, Entry 3. A weakly electron attracting group such as bromine, Entry 4, retards the reaction only slightly, if at all, while a strongly electron attracting group, nitro, Entry 5, inhibits the reaction completely. Inhibition of the reaction by the presence of bulky groups in the ortho positions, Entries 6 and 7, is also consistent with an S_N2 mechanism. Aromatic diamines, 1,4-phenylenediamine

and 1,2-phenylenediamine, Entries 8 and 9, react with ethylene sulfate to form only mono adducts. Even when two moles of ethylene sulfate are used per mole of diamine only the mono adduct forms. Benzylamine reacts in high yield with ethylene sulfate, Entry 10, as do aliphatic amines such as octylamine, *t*-butylamine, and cyclopropylamine, Entries 11-13. Aliphatic diamines such as ethylenediamine and piperazine react with one mole of ethylene sulfate in high yield, Entries 14 and 15. An excess of ethylene sulfate gives no diadduct. Ammonia, bubbled through a methylene chloride solution of ethylene sulfate, affords β -aminoethyl sulfate in high yield, Entry 16.

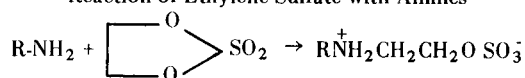
Carbon-oxygen bonds may be formed by the reaction of ethylene sulfate with phenolates, carboxylates and amine oxides. Sodium or potassium phenolate reacts quantitatively with ethylene sulfate in refluxing methylene chloride in four hours, Reaction II, R = H. Potassium 4-methoxyphenolate also reacts quantitatively with ethylene sulfate.



The reaction of benzoic acid with ethylene sulfate, a slurry in refluxing methylene chloride with an equivalent amount of potassium carbonate, Reaction III, R = H, occurs much less readily than the reaction of ethylene sulfate with phenolates. β -Benzoxyethyl sulfate is formed

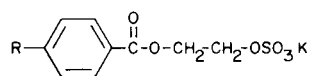
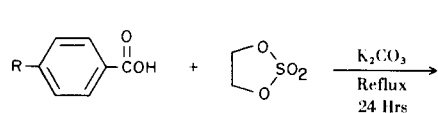
TABLE I

Reaction of Ethylene Sulfate with Amines

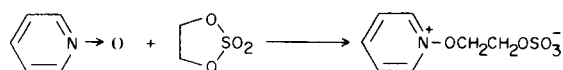


Entry	Amine	Reaction Time (Hours)	% Yield	M.p., °C
1	Aniline	4	95	202-204
2	4-Methylaniline	4	96	124-125
3	4-Methoxyaniline	4	93	240-241
4	4-Bromoaniline	4	92	231-232
5	4-Nitroaniline	4	No Reaction	
6	2,6-Dimethylaniline	23	97	> 250
7	2,6-Dibromoaniline	45	19	> 250
8	1,4-Phenylenediamine	4	74	> 250
9	1,2-Phenylenediamine	4	96	170-172
10	Benzylamine	17	>98	244-246
11	Octylamine	17	>90	Amorphous Solid
12	<i>t</i> -Butylamine	4	99	> 250
13	Cyclopropylamine	4	>90	Amorphous Solid
14	Ethylenediamine	4	90	Viscous Oil
15	Piperazine	4	70	Viscous Oil
16	Ammonia	6	>90	

in a 50% yield after 24 hours. *p*-Nitrobenzoic acid is unreactive toward ethylene sulfate, Reaction III, R = NO₂.



One example of carbon-oxygen bond formation *via* an amine oxide-ethylene sulfate reaction was observed, Reaction IV. Pyridine oxide and ethylene sulfate react in

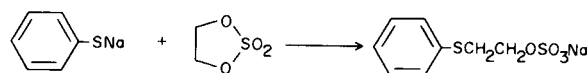


refluxing methylene chloride in 24 hours to give a quantitative yield of 1-(2-hydroxyethoxy)pyridinium hydroxide, hydrogen sulfate, inner salt. This reaction represents another example of an uncommon type of reaction, the *O*-alkylation of amine oxides (7). Although, as early as

1896 (8), trimethylamine oxide was *O*-methylated with methyl iodide, our study represents the first *O*-alkylation of an amine oxide by another alkylating agent.

β -Substituted ethyl sulfates are formed by the reaction of ethylene sulfate with metal salts of hydrocarbons. Dimethylmalonate sodium, phenylethynyllithium, and phenyllithium react in near quantitative yield with ethylene sulfate, Table II.

Carbon-sulfur bond formation may be accomplished by the reaction of ethylene sulfate with sodium thiophenolate, Reaction V. The reaction is carried out in

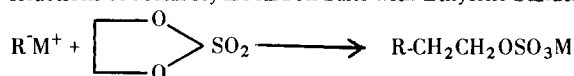


refluxing methylene chloride for seventeen hours. The product, sodium β -thiophenoxyethyl sulfate, precipitates quantitatively.

β -Substituted ethyl sulfates undergo a number of interesting reactions. They are stable in hot and cold water for short times and may be recrystallized from water/dioxane. However, hydrolysis occurs in 2 *N* sulfuric acid at 80-90° in one hour to form the corresponding alcohols in yields

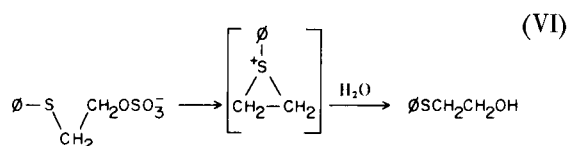
TABLE II

Reactions of Metal Hydrocarbon Salts with Ethylene Sulfate

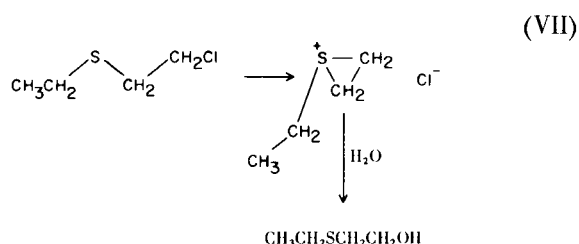


R^-M^+	Product	Reaction Time (Hours)	% Yield
$Na^+ \dot{C}H(CO_2CH_3)_2$	$\begin{array}{c} CH(CO_2CH_3)_2 \\ \\ CH_2CH_2OSO_3Na \end{array}$	20	> 95
$\text{C}_6\text{H}_5\text{C}\equiv\text{C}^-Na^+$	$\text{C}_6\text{H}_5\text{C}\equiv\text{CCH}_2\text{CH}_2OSO_3Na$	20	> 95
$\text{C}_6\text{H}_5\text{Li}$	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2OSO_3Li$	3	> 95

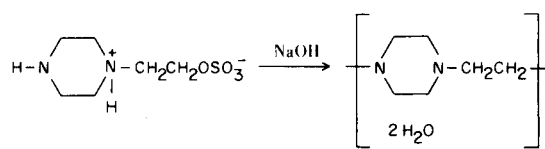
of 70-80%. β -Anilinoethyl sulfate inner salt, β -(4-aminoanilino)ethyl sulfate inner salt, sodium β -(phenylethynyl)ethyl sulfate, lithium phenethyl sulfate, and sodium β -thiophenoxyethyl sulfate hydrolyze to their respective alcohols in this manner. An unexpected reaction occurs when an attempt is made to recrystallize sodium β -thiophenoxyethyl sulfate from water/dioxane. Sodium sulfate and β -thiophenoxyethyl alcohol form readily during recrystallization. This reaction does not occur when the sulfur atom of the thiophenol moiety is replaced by oxygen. This facile hydrolysis may be rationalized in terms of a neighboring group effect involving the sulfur atom. A cyclic sulfonium ion may be formed which would react rapidly with water forming β -thiophenoxyethyl alcohol, Reaction VI.



This interpretation is consistent with the hydrolysis of the β -chloro sulfide, $\text{ClCH}_2\text{CH}_2\text{SCH}_2\text{CH}_3$, which hydrolyzes 10,000 times as rapidly as the corresponding ether, $\text{ClCH}_2\text{CH}_2\text{OEt}$. The rate enhancement is attributed to the formation of a transient sulfonium ion, Reaction VII (9).

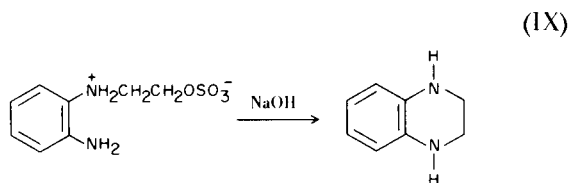


In special cases ethylene sulfate adducts may be polymerized by treatment with sodium hydroxide, Reaction VIII. Treating β -(diethylenediamino)ethyl sulfate with 2 *N* sodium hydroxide at 95° for one hour produces a white polymer, m.p. > 250°. An elemental analysis of this material, although not exact, indicates 2 moles of water per repeating unit. This material is insoluble in organic solvents but soluble in hot water. Heating the polymer at



100° (1 mm) for 17 hours gives a new compound. The elemental analysis of this material, although not exact, indicates a mono hydrate. The polymer is similar to the polymer synthesized by Giuseppe and Cantatore from piperazine and ethylene chloride (10). Treatment of β -ethylenediaminoethyl sulfate, $\text{H}_2\text{NCH}_2\text{CH}_2\text{N}^+\text{H}_2\text{CH}_2\text{CH}_2\text{OSO}_3^-$, with 2 *N* sodium hydroxide also affords a white polymer which melts > 250°. This material is insoluble in organic solvents but soluble in hot water. The elemental analysis of the polymer is consistent with polyethylenimine containing one mole of carbon dioxide and one mole of water per mole of ethylenimine.

An interesting ring closure reaction occurs when the ethylene sulfate adduct, β -(2-aminoanilino)ethyl sulfate, is treated with 2 *N* sodium hydroxide at 80-90° for two hours, Reaction IX. 1,2,3,4-Tetrahydroquinoxaline is formed in 58% yield.



In conclusion, the synthesis of substituted ethyl sulfates and their reactions with nucleophilic reagents has been discussed. Rapid reaction of ethylene sulfate occurred with amines, phenolates, carboxylates, amine oxides, carbanions, and thiophenolates to form β -substituted ethyl sulfates. β -Substituted ethyl sulfates were easily hydrolyzed and in some cases were polymerized.

EXPERIMENTAL

Ethylene sulfate was prepared according to the method of J. Brunken (11). Other reactants and solvents were commercial samples and were not further purified prior to use. The products isolated from the reactions of ethylene sulfate with the nucleophilic reagents described in this paper were characterized by elemental analysis and infrared and nmr spectra. Wherever possible, comparisons were made with authentic samples.

Amine-Ethylene Sulfate Adducts.

In a typical reaction ethylene sulfate, 12.4 g. (0.10 mole), and aniline, 9.3 g. (0.10 mole), were dissolved in 75 ml. of methylene chloride. The mixture was refluxed for four hours. β -Anilinoethyl sulfate precipitated from the refluxing solution. The cooled slurry was filtered and the solid recrystallized from water/dioxane to give 19.1 g. (0.095 mole, 95% yield) of β -anilinoethyl sulfate, m.p. 202-204°.

Anal. Calcd. for $C_8H_{11}NSO_4$: C, 44.2; H, 5.07; N, 6.45; S, 14.75. Found: C, 44.4; H, 5.19; N, 6.42; S, 14.80.

Oxide-Ethylene Sulfate Adducts.

A solution was made of 5.6 g. (0.10 mole) of potassium hydroxide and 9.4 g. (0.10 mole) of phenol in 50 ml. of methanol. The methanol and water was removed from the potassium phenolate by heating on the steam bath under a vacuum of 25 mm. for three hours. Ethylene sulfate, 12.4 g. (0.10 mole), dissolved in 100 ml. of methylene chloride was added to the potassium phenolate. The slurry was refluxed for four hours. The cooled slurry was filtered and the solid recrystallized from water/dioxane to give 25.0 g. (0.097 mole, 97% yield) of β -phenoxyethyl sulfate, m.p. > 250°.

Anal. Calcd. for $C_8H_9SO_5K$: C, 37.5; H, 3.52; S, 12.50. Found: C, 37.2; H, 3.61; S, 12.8.

Carbanion-Ethylene Sulfate Adducts.

A slurry was made of 12.4 g. (0.10 mole) of ethylene sulfate in 150 ml. of ether. This slurry was cooled to 5° and 42 ml. of a 20% solution of phenyllithium (8.4 g., 0.10 mole) in

ether/benzene was added. The slurry was allowed to warm to room temperature and then was refluxed for three hours. The slurry was filtered to give 19.7 g. (0.095 mole, 95% yield) of lithium phenethyl sulfate. The structure of lithium phenethyl sulfate was determined by hydrolysis with 2 *N* sulfuric acid to give β -phenethyl alcohol, a known compound.

Hydrolysis of Ethylene Sulfate Adducts.

Lithium β -phenethyl sulfate, 11.1 g. (0.053 mole), was dissolved in 100 ml. of 2 *N* sulfuric acid. The solution was heated at 80-90° for one hour. The cooled solution was extracted with several portions of methylene chloride; the methylene chloride solution was dried over magnesium sulfate, and the solvent was removed by distillation. β -Phenethyl alcohol, 4.8 g. (0.04 mole, 75% yield) was isolated. The infrared and nmr spectra of the material were identical to the spectra of an authentic sample obtained from Eastman Kodak.

Anal. Calcd. for $C_8H_{10}O$: C, 78.7; H, 8.2. Found: C, 78.0; H, 8.18.

Polymerization of Ethylene Sulfate Adducts.

β -(Diethylenediamino)ethyl sulfate, 10.4 g. (0.05 mole), was dissolved in 50 ml. of 2 *N* sodium hydroxide. The solution was heated at 95° for two hours. During this time a white precipitate formed which was filtered and recrystallized from water. Two and eight tenths g. of 1,4-piperazinediylethyleneamer containing two moles of water per subunit was isolated, 50% conversion, m.p. > 250°. Heating the dihydrate at 100° (0.1 mm) for 17 hours gave the monohydrate.

Anal. Calcd. for $C_6H_{12}N_2 \cdot 2H_2O$: C, 48.7; H, 10.8; N, 18.9. Found: C, 48.0; H, 8.94; N, 19.1.

Anal. Calcd. for $C_6H_{12}N_2 \cdot H_2O$: C, 55.4; H, 10.8; N, 21.6. Found: C, 56.0; H, 9.62; N, 22.3.

REFERENCES

- (1) Author to whom all correspondence should be addressed. Current address: Roy C. Ingersoll Research Center, Borg-Warner Corporation, Des Plaines, Illinois 60018.
- (2) E. T. Kaiser, M. Panar, F. H. Westheimer, *J. Am. Chem. Soc.*, **85**, 602 (1963).
- (3) E. T. Kaiser, I. R. Katz, and T. F. Wulfers, *ibid.*, **87**, 3781 (1965).
- (4) O. R. Zaborsky and E. T. Kaiser, *ibid.*, **88**, 3084 (1966).
- (5) E. B. Fleischer, E. T. Kaiser, P. Langford, S. Hawkinson, A. Stone, and R. Dewar, *Chem. Commun.*, 197 (1967).
- (6) F. P. Boer, J. J. Flynn, E. T. Kaiser, O. R. Zaborsky, D. A. Tomalia, A. E. Young, Y. C. Tong, *J. Am. Chem. Soc.*, **90**, 2970 (1968).
- (7) C. C. J. Culvenor, *Revs. Pure and Appl. Chem. (Australia)*, **3**, 83-114 (1953).
- (8) W. R. Dunstan and E. Goulding, *Trans. Chem. Soc.*, **69**, 839 (1896); *ibid.*, **71**, 573 (1897); **75**, 793, 1004 (1899).
- (9) Bohme and Sell, *Chem. Ber.*, **81**, 123 (1948).
- (10) Giuseppe and Cantatore, Belgium Patent, 632,727, November 22, 1963; *Chem. Abstr.*, **61**, 768e (1963).
- (11) J. Brunken, West German Patent, 1,049,870 (1959).