[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

Sulfur Studies. XVI. The Synthesis of Certain Higher Alkyl Sulfonium Salts and Related Compounds

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The ability of dialkyl sulfides to react with alkyl iodides with the subsequent formation of sulfonium iodides has been known for many years[3,4]; however, most of the earlier work was confined chiefly to the lower dialkyl sulfides. Within recent years the higher alkyl halides have become available commercially, thus allowing an extension of this work to sulfides of fairly high molecular weight.

The alkyl sulfonium compounds have certain chemical and physiological properties in common with the alkyl ammonium compounds, consequently the problem of studying these compounds becomes more engaging. The physiological activity of certain sulfonium compounds has been investigated by Renshaw and co-workers[5,6,7,8] and also by Ing and Wright.[9] These workers found that sulfonium analogs of betaine and choline produce similar effects, but are less active.

In this work attention was directed toward the preparation of sulfonium compounds of the type $\left(R-S{\overset{R'}{\underset{R''}{\diagdown}}} \right)^+ X^-$, where R is $C_{12}H_{25}$ or $C_{16}H_{33}$, R' is C_2H_5 and R'' is CH_3; X may be Br, I or NO_3. The mercuric chloride and bromide addition compounds of ethyl cetyl sulfide were also prepared as well as the sulfones of the aforementioned sulfides. The pharmacological studies have been carried out by the Wm. S. Merrell Company of Cincinnati through the courtesy of Dr. Robert S. Shelton and will be reported elsewhere.

Some difficulty was experienced in the earlier stages of this work in finding a suitable medium for carrying out the reaction between the alkyl sulfides and methyl iodide. Carrara[10] studied the kinetics of the reaction between alkyl sulfides and ethyl iodide and found the reaction to be of the second order. He also studied the effects of a few of the lower alcohols and acetone on the re-

action. From the few solvents studied he found, in general, that solvents of high dielectric constant seem to favor the reaction but the parallel is not very close. According to Carrara, acetone, which has a fairly high dielectric constant, definitely retards the reaction. Richardson and Soper[11] attempted to predict the velocity of a reaction similar to the one under consideration from data on the "cohesion" of the solvent. There does not ·seem, however, to be any standard method of evaluating "cohesions," and the various methods now in use give widely varying results.

It was therefore deemed advisable to extend further the work on the effect of solvent on sulfonium halide formation. After studying the reaction of ethyl cetyl sulfide and methyl iodide in fourteen different solvents as shown in Table I, methanol was found to be the best reaction medium when yields, purity of products and ease of isolation are taken into consideration. Since the alkyl sulfonium compounds are hygroscopic and water soluble, some difficulty was also experienced in isolating the crude sulfonium salt, but, once isolated, the purification was relatively simple as long as anhydrous solvents were used.

Experimental

Sulfides.—The unsymmetrical sulfides used in the sulfonium preparations were made by the method of Beckmann[12] as modified by Belcher.[13] The sodium mercaptide is prepared by dissolving an equivalent weight of sodium hydroxide in the smallest possible quantity of water, diluting with alcohol and then adding an equivalent weight of mercaptan. No attempt was made to isolate the sodium mercaptide. The alkyl halide (one mole) was added to the alcohol solution with external cooling. There was no precipitation of sodium bromide, due to the large amount of water present, but the fact that reaction was taking place was demonstrated by the vigorous boiling ensuing at this point. The mixture was refluxed for four hours and allowed to cool. The sulfide separated as an oil having almost the same specific gravity as the aqueous alcoholic sodium bromide solution. In the case of ethyl cetyl sulfide, the oil was chilled at this point to 0°, causing the oil to solidify. The aqueous solution was poured off. Dilution of the aqueous layer with water and extraction with light petroleum

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(4) Cahours, *ibid.*, 352 (1865).
(5) Rencowitz and Renshaw, THIS JOURNAL, **47**, 1904 (1925).
(6) Renshaw and Bacon, *ibid.*, **48**, 1726 (1926).
(7) Hunt and Renshaw, *J. Pharmacol.*, **25**, 315 (1925).
(8) Hunt and Renshaw, *ibid.*, **44**, 63 (1932).
(9) Ing and Wright, *Proc. Roy. Soc.* (London), **B114**, 46 (1933).
(10) Carrara, *Gazz. chim ital.*, **24**, I, 180 (1894).

(11) Richardson and Soper, *J. Chem. Soc.*, II, 1873 (1929).
(12) Beckmann, *J. prakt. Chem.*, **17**, 457 (1878).
(13) R. Belcher, "The Preparation and Properties of Certain Mixed Sulfides," Thesis, University of North Carolina, 1931.

showed that it contained almost none of the sulfide. The oil layer was washed with water to remove any adhering sodium bromide. The ethyl lauryl sulfide, having a lower melting point, could not be isolated in this way. It was thrown out of solution by addition of an equal volume of water and extracted with three portions of light petroleum. In each case the petroleum solution of the sulfide was dried over anhydrous sodium sulfate and the petroleum removed on a steam-bath. The sulfides were fractionated under reduced pressure.

For analysis it was necessary to purify further the sulfide by making use of the mercuric chloride addition compounds of the sulfides. These addition compounds were decomposed by the method of Faragher, Morrell and Comay[14] for analyzing this type of compound. The addition compound is treated with four equivalents of an 18% solution of sodium thiosulfate and boiled for five minutes. A concentrated solution of sodium sulfide is added until a clear solution is obtained. The mixture is then cooled and the sulfide extracted with light petroleum ether. This solution is dried as above, concentrated and distilled.

Sulfones.—The sulfones were prepared by the method of Bost and Conn.[15] The sulfide is dissolved in a minimum amount of glacial acetic acid and treated with a 50% excess of a saturated aqueous solution of potassium permanganate. The permanganate is added gradually with cooling and the mixture allowed to stand for two hours after completion of the addition. The solution is then decolorized by adding concentrated sodium bisulfite solution, with care to avoid an excess. The mixture is then chilled and filtered. The sulfones were recrystallized from dilute alcohol until constant melting points were reached.

Mercuric Halide Addition Compounds.—The mercuric halide addition compounds were prepared by mixing saturated alcoholic solutions of the components and allowing the mixture to stand until complete precipitation took place. The product was recrystallized for analysis from dilute alcohol.

Preparation of Sulfonium Compounds. Effect of Solvent on Sulfonium Iodide Formation.—In order to decide upon a suitable solvent for the preparation of sulfonium compounds, mixtures were prepared of ethyl cetyl sulfide and methyl iodide in various solvents and heated for two hours. A ten mole excess of the iodide was used, since a certain amount of loss was to be expected on account of the volatility of this reagent. In all cases 0.9 g. of sulfide, 4.45 g. of the iodide and 1 cc. of solvent were used, except where otherwise noted in Table I.

Sulfonium Iodides.—The sulfonium iodides were prepared by dissolving the sulfides in methanol and adding a five to ten mole excess of methyl iodide. The mixture is placed in a flask equipped with a long (5-foot) reflux condenser and heated on the steam-bath for four hours. The solution is then concentrated to small volume on the steam-bath and the iodide precipitated by addition of absolute ether. The product is dried in a vacuum desiccator and purified by dissolving in the smallest possible quantity of absolute alcohol and precipitating with three volumes of absolute ether. Usually one such precipitation, followed

(14) Faragher, Morrell and Comay, THIS JOURNAL, **51**, 2774–81 (1929).

(15) Bost and Conn, Ind. and Eng. Chem., **23**, 93 (1931).

TABLE I
METHYL ETHYL CETYL SULFONIUM IODIDE FORMATION IN VARIOUS SOLVENTS[a]

Solvent	Dielectric[b] constant	Yield, g.	M. p., °C.	Color of product
None	. . .	0.6	70	Light yellow
Nitrobenzene	34.09	.43	69	Yellowish
Methanol (5 cc.)	31.2	.9	72	White
Ethanol (3.5 cc.)	25.8	.9	72	White
Acetone	21.5	.64	71	Very white
Benzyl alcohol	13.0	.58	68	Yellow
Acetic acid	6.13	.71	70	White
Ethyl acetate	6.11	.29	70	Yellowish
Chloroform	4.64	.51	71	White
Ethyl ether	4.35	.23	69	Yellowish
Carbon disulfide	2.67	.24	71	White
Benzene	2.29	Trace	..	White
Dioxane	2.23	0.27	71	White
Carbon tetrachloride	2.21	.26	67	Yellow
β,β'-Dichlorodiethyl ether	. . .	.08	68	Orange

[a] Pure methyl ethyl cetyl sulfonium iodide melts at 73°.
[b] Values for the dielectric constants were taken from "Organic Solvents," by Weissberger and Proskauer, Oxford Press, New York, N. Y., 1935.

by drying in the desiccator, gives a compound of constant melting point.

Sulfonium Bromides.—The sulfonium bromides were prepared by the same method as that given for the iodides, with the use of a methanol solution of methyl bromide in place of the methyl iodide. In this case the heating was continued for a longer time (three–four days). The product was isolated as described for the iodides.

Sulfonium Nitrates.—For preparation of a sulfonium nitrate, the sulfonium iodide is dissolved in absolute alcohol and treated with an exactly equivalent amount of silver nitrate in the same solvent. The precipitate is removed by filtration and any excess silver in solution removed by treatment with hydrogen sulfide. The solution is boiled to coagulate the silver sulfide precipitate and filtered again to remove the coagulate. The resulting solution is concentrated to small volume and the sulfonium nitrate precipitated from the cooled solution with absolute ether. Purification and drying are the same as for the iodides and bromides.

Analysis.—The sulfonium halides were analyzed for halogen by direct titration with silver nitrate solution, using the Volhard method. The sulfonium halide is dissolved in 95% alcohol and the solution diluted to 50 cc. An excess (25 cc.) of 0.05 normal silver nitrate solution is added and the mixture boiled to coagulate the precipitate. Nitric acid (10 cc., 6 N) and ferric alum indicator solution (5 cc.) are added, and the solution diluted to 150 cc. In the case of iodides it is essential that the halide be completely precipitated before the indicator is added, as otherwise a partial oxidation of the iodide ion takes place. The excess of silver nitrate is titrated with standard (0.05 N) potassium thiocyanate solution.

All other sulfur-containing compounds were analyzed for sulfur by the usual Parr bomb procedure.

In Table II will be found data on the compounds prepared by the above procedures.

TABLE II

SULFIDES

Compound	M. p., °C.	B. p., °C.	%S Calcd.	%S Found
Ethyl cetyl sulfide	19	201–205 (12 mm.)	11.19	11.34
Ethyl lauryl sulfide	−6 to −5	167–171 (18 mm.)	13.91	14.14

Mercuric Halide Addition Compounds

Ethyl cetyl sulfide mercuric chloride	75.5		5.75	5.17
Ethyl cetyl sulfide mercuric bromide	58		4.95	5.21

Sulfones

Ethyl cetyl	88		10.06	10.18
Ethyl lauryl	78.5		12.22	12.24

Sulfonium Nitrate

Methyl ethyl cetyl	61		8.82	8.75

Sulfonium Halides

Compound	M. p., °C.	% Halogens Calcd.	% Halogens Found
Methyl ethyl cetyl sulfonium iodide	73	29.62	29.61
Methyl ethyl cetyl sulfonium bromide	77	20.95	20.68
Methyl ethyl lauryl sulfonium iodide	65	34.08	33.92

Summary

1.   Two new unsymmetrical dialkyl sulfides have been prepared and characterized by their sulfones and mercuric halide addition products.

2.   These sulfides readily form sulfonium salts under suitable conditions.

3.   Methanol was found to be the best solvent for sulfonium halide formation.

4.   In general, with the exception of nitrobenzene, solvents possessing a high dielectric constant favor the reaction for sulfonium halide formation, from the standpoint of yield, purity of product and ease of isolation. The paradoxical behavior of acetic acid in this connection is also noted.

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RECEIVED MARCH 4, 1940

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Synthesis of Certain Trisaccharides and a Study of their Behavior in Alkaline Solution[1,2]

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In an aqueous solution of potassium hydroxide maltose is converted into approximately one-half as much lactic acid as an equivalent solution of d-glucose under the same experimental conditions.[4]

To explain this difference in yields, Evans and Benoy advanced the following suggestions. (a) The reducing section of the maltose molecule is degraded with the formation of either formaldehyde or glycol aldehyde, and either 3-glucosido-arabinose or 2-glucosido-erythrose, respectively.

(b) The 3-glucosido-arabinose may also undergo fragmentation to formaldehyde and 2-glucosido-erythrose.   (c) The final 2-glucosido-erythrose was then believed to undergo alkaline hydrolysis to erythrose and glucose.   (d) Since formaldehyde, glycol aldehyde and erythrose produce no lactic acid under our experimental conditions and, on the other hand, glucose does, it is evident that only one-half of the maltose molecule is yielding lactic acid, and that that half is the glucosido section, that is, the non-reducing section of the molecule. The investigations of Evans and co-workers[5] were extended to other disaccharides and to oligosaccharides in the dihydroxyacetone series in order to find further evidence for the above suggested mechanism.

(1) The material of this paper has been abstracted from a thesis submitted by Samuel Harding Nichols, Jr., to the Graduate School of The Ohio State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1939.

(2) An abstract of this paper was presented at the Baltimore meeting of the American Chemical Society in 1939.

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(4) W. L. Evans and M. P. Benoy, THIS JOURNAL, 52, 294 (1930).

(5) H. Gehman, L. C. Kreider and W. L. Evans, ibid., 58, 2388 (1936).