Attempts to make the Grignard reagent from the *o*- and *p*-bromobenzyl methyl ethers in order to form the corresponding triaryl bismuthines were unsuccessful.

Summary

1. A method has been developed for oxidizing tritolyl-bismuth dihalides to the corresponding carboxy compounds.

2. Various nitro-triaryl bismuthines and bismuth dihalides have been prepared.

3. A careful study of the reduction of triaryl bismuth dihalides to triaryl bismuthines has been completed with the result that sodium hydrosulfite has proved to be a very satisfactory reagent.

4. Preliminary work on sulfonation of triaryl bismuth dihalides is reported.

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[CONTRIBUTION FROM THE HAVEMEYER CHEMICAL LABORATORY OF NEW YORK UNIVERSITY]

THE BASIS FOR THE PHYSIOLOGICAL ACTIVITY OF CERTAIN -ONIUM COMPOUNDS[1,2]

IV. THE SULFUR ANALOG OF CHOLINE

BY R. R. RENSHAW, N. BACON AND J. H. ROBLYER

RECEIVED NOVEMBER 5, 1925 PUBLISHED FEBRUARY 5, 1926

Little work seems to have been reported on the preparation of substituted alkyl sulfonium derivatives. It is possible that this is due to the fact that the sulfonium compounds with a few exceptions are much more slowly formed and are very much less stable than many of the other -onium compounds. This instability is associated with the ready dissociation of the -onium structure.

It has been shown that when a number of different halogen compounds are heated with dimethyl sulfide, trimethylsulfonium halides are formed. Cahours[3] demonstrated this fact with methylene iodide, ethylene bromide, acetyl iodide and bromocyanogen and Carrara[4] with iodine. The mechanism in these cases was undoubtedly similar to the one operating when Klinger and Maassen[5] obtained trimethylsulfonium iodide by distilling both dimethyl-ethylsulfonium iodide and methyl-diethylsulfonium iodide.

It seems clear from the results of these earlier investigators and from

[1] Study of this problem is being carried on in coöperation with Dr. Reid Hunt of the Harvard Medical School. The physiological data are the basis of another series of papers published elsewhere by him.

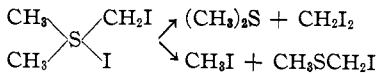
[2] A general discussion of this problem may be found in the introductory paper, *Sci.*, **62**, 384 (1925).

[3] Cahours, *Ann. chim. phys.*, [5] **10**, 29 (1878).

[4] Carrara, *Gazz. chim. ital.*, **22**, I, 408 (1892).

[5] Klinger and Maassen, *Ann.*, **252**, 246 (1889).

our own work that the -onium structure is first formed and that this then undergoes two different dissociations. This may be illustrated in the case of the action of methylene iodide on dimethyl sulfide.



These products then combine in a different manner and due to the greater rate of formation of the trimethylsulfonium salt, a considerable quantity of this substance is quickly formed.

$$(CH_3)_2S + CH_3I \longrightarrow (CH_3)_3SI;\ CH_3SCH_2I + CH_2I_2 \longrightarrow CH_3SI(CH_2I)_2$$

We have found that this particular dissociation takes place so rapidly in alcohol at 50° that it is impossible to purify the crude iodo compound by recrystallization from this solvent. A very marked tendency for such transformations to take place has been observed also in our work on the sulfur analog of choline.

It has long been thought that the quaternary compounds of nitrogen, phosphorus, arsenic and antimony as well as the simple sulfonium compounds have a curare-like action on the motor nerve endings. This action has been cited as one which is independent of the -onium element.[6] Since the curare effect is given by a variety of substances it seemed desirable to determine whether the -onium element is significant with regard to other physiological effects (the muscarine and the nicotine effects) which appear to be more characteristic of the alkyl and substituted alkyl -onium compounds of nitrogen. A number of derivatives of these elements which have been prepared in this Laboratory have been tested by Hunt.[7] By means of them he has been able to get more specialized control over the peripheral nervous system than has been possible previously. The results indicate that the -onium element may determine very largely the degree and to some extent also the type of the particular physiological effect. While the completely methylated -onium derivatives of nitrogen, phosphorus and sulfur have an intense, stimulating, nicotine action, the derivatives of arsenic and antimony in larger doses did not give this action. On the other hand, all these derivatives give the muscarine effect although in a markedly varying degree.

The present paper deals with the synthesis of certain sulfur analogs of choline. When dimethyl sulfide is heated with β-chloro- or iodo-ethyl alcohol or with β-bromo- or iodo-ethyl acetate in alcohols, ether or toluene, or without a solvent, considerable amounts of trimethylsulfonium salts are formed. In the filtrates from this substance, there were found materials

[6] It should be noted that Hunt (Ref. 7, p. 325) did not get a currae effect on the motor nerve endings of the frog with amounts of the tetramethyl derivatives of arsenic and antimony 75 and 150 times as great, respectively, as was required of the tetramethylammonium ion to give distinct paralysis.

[7] Hunt and Renshaw, *J. Pharm. Exptl. Therap.*, **25**, 315 (1925).

forming highly hygroscopic, difficultly crystallizable oils which from analytical data appeared to be mixtures containing either bis hydroxyethyl-methylsulfonium salts or the corresponding acetyl derivatives. These products were probably formed in the manner suggested in the foregoing.

A mixture of dimethyl sulfide and β-bromo-ethyl acetate had not completely reacted after four months' standing at room temperature, and the product formed was a mixture containing considerable trimethylsulfonium bromide.

Hydroxyethyl-dimethylsulfonium Iodide, $(CH_3)_2S(I)CH_2CH_2OH$.—When a mixture of 9 g. of dimethyl sulfide and 25 g. of β-iodo-ethyl alcohol was allowed to stand in the dark at room temperature for several days, a thick, dark brown sirup resulted. By repeatedly washing this with ethyl acetate and acetone a colorless oil was obtained which crystallized in long, needle crystals after standing for a few hours in a vacuum desiccator. The crystals were very hygroscopic and soon decomposed on standing.

The somewhat low analytical values were probably due to the appreciable dissociation of the substance in the vacuum treatment found necessary in purification.

Anal. Calcd. for $C_4H_{11}OSI$: I, 54.27. Found: 53.83, 53.90.

Acetoxymethyl-dimethylsulfonium Bromide, $(CH_3)_2S(Br)CH_2OOCCH_3$.—A mixture of 4.5 cc. each of dimethyl sulfide and bromomethyl acetate was allowed to stand. After about 30 minutes a thick, orange-colored oil had separated and colorless crystals had begun to form. The clear liquid was decanted from the oil. After several hours it had almost completely solidified. The solid product was then washed repeatedly with anhydrous ether, dissolved in cold absolute ethyl alcohol by triturating in a mortar with that solvent, and quickly precipitated from this solution with dry ether. So formed, this sulfonium compound crystallized in aggregates of needle plates resembling cart wheels. These are easily soluble in water and methyl alcohol and only moderately soluble in absolute ethyl alcohol. They melt at 104° (corr.). In the presence of any foreign material or moisture the substance decomposes on standing. When heated in alcohol solution it rapidly alcoholizes and then dissociates giving off a strong odor of dimethyl sulfide and formaldehyde.

Anal. Calcd. for $C_5H_{11}O_2SBr$: Br, 37.2. Found: 36.99, 36.94.

Hunt[8] has found that this sulfonium compound has a very intense muscarine action though not quite so strong as the corresponding nitrogen derivative (acetoxymethyl-trimethylammonium bromide). On the other hand, in comparatively large doses there was a complete absence of evidence of any stimulating nicotine effect. The nitrogen analog in one-half the dosage gave this action very markedly. These results show clearly that with these two analogous compounds of sulfur and nitrogen, the -onium element determines, if not actually the type of action (stimulating, nicotine effect), then certainly to an extraordinary degree the extent.

The authors wish to express their appreciation to the Directors of the Bache Fund, National Academy of Sciences, for a grant made to support this investigation.

Summary

1. The sulfur analog of choline (hydroxyethyl-dimethylsulfonium iodide) and of acetyl formocholine (acetoxymethyl-dimethylsulfonium bromide) have been prepared.

[8] Ref. 7, pp. 337–338.

2. The pharmacological examination of the latter substance indicates that the -onium element is significant in determining the stimulating, nicotine effect.

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SOME DERIVATIVES OF ETHYL SELENOMERCAPTAN

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RECEIVED NOVEMBER 7, 1925 PUBLISHED FEBRUARY 5, 1926

Introduction

The original object in taking up the study of ethyl selenomercaptan was to obtain selenium compounds similar to sulfonal.[2] This object was not attained because the mercaptole skeleton $R_2>C<(SeC_2H_5)_2$ is broken up by oxidation. Owing to the fact that very little study has been made of derivatives of ethyl selenomercaptan, it was considered advisable to broaden the scope of the investigation, and study several reactions of ethyl selenomercaptan.

Historical

Ethyl selenomercaptan was first prepared by Siemens[3] in 1847, who proved his product to be a mercaptan by allowing it to react with mercuric oxide to form the mercury-ethyl selenomercaptide, $(C_2H_5Se)_2Hg$. Tschugaeff[4] has also studied the reactions of aliphatic selenomercaptans, preparing mercaptides and mixed aliphatic seleno-ethers. He also observed the fact that aliphatic selenomercaptans can be readily oxidized by atmospheric oxygen to the corresponding diselenides. No further work has been reported on the reactions of aliphatic selenomercaptans.

Outline of the Present Investigation

I. The preparation of ethyl selenomercaptan.

$$C_2H_5NaSO_4 + NaSeH \longrightarrow C_2H_5SeH + Na_2SO_4$$

II. The condensation of ethyl selenomercaptan with ketones.

$$R_2>CO + 2HSeC_2H_5 \longrightarrow R_2>C<(SeC_2H_5)_2 + H_2O$$

III. The oxidation of the mercaptoles.

$$R_2>C<(SeC_2H_5)_2 + HNO_3 \longrightarrow 2C_2H_5SeO_2H.HNO_3$$

IV. The reaction of sodium ethyl selenomercaptide with β,β'-dichloroethyl sulfide, sulfoxide and sulfone.

$$S(CH_2CH_2Cl)_2 + 2NaSeC_2H_5 \longrightarrow S(CH_2CH_2SeC_2H_5)_2 + 2NaCl$$
$$OS(CH_2CH_2Cl)_2 + 2NaSeC_2H_5 \longrightarrow OS(CH_2CH_2SeC_2H_5)_2 + 2NaCl$$
$$O_2S(CH_2CH_2Cl)_2 + 2NaSeC_2H_5 \longrightarrow O_2S(CH_2CH_2SeC_2H_5)_2 + 2NaCl$$

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[1] From the Doctor's Dissertation of Edwin H. Shaw, Jr., 1925.

[2] Baumann, *Ber.*, **19**, 2808 (1886).

[3] Siemens, *Ann.*, **61**, 360 (1847).

[4] Tschugaeff, *Ber.*, **42**, 49 (1909).