[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF CENTRE COLLEGE, KENTUCKY, AND OF WEST VIRGINIA UNIVERSITY.]

A STUDY OF CHLORO ETHERS. I. THE ACTION OF CHLORODIMETHYL ETHER ON SALTS OF ORGANIC ACIDS.

BY FRIEND E. CLARK, S. F. COX AND E. MACK.

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The usefulness of the chloro ethers as mediums in synthetic studies has often been noted. For example, Litterschied and Thimme[1] have studied and formulated in one paper alone the reactions of chlorodimethyl ether with twelve organic compounds. Bayer & Company,[2] in 1903, were granted a patent for the preparation of an alkyl ester of salicylic acid, involving the use of chlorodimethyl ether. Gomberg[3] employed the same compound in the condensation of triphenylmethyl to hexaphenylethane. Among the other pieces of work done on the chloro ethers are those of Gaspari[4] and Wedekind[5] on the reactions with the salts of organic acids.

Gaspari heated (at 130°) chloromethylethyl ether with fused sodium acetate in a flask with a return condenser. The reaction was

$$CH_3COONa + ClCH_2OC_2H_5 = CH_3COOCH_2OC_2H_5 + NaCl.$$

The boiling point of this acetate of chloromethylethyl ether is given as 130–131° and the density as 1+. Wedekind investigated the action of chloromethylethyl ether on potassium acetate and lead formate. In speaking of his products, he says that "they boil somewhat above a hundred degrees." Such obvious incompleteness led us to take up the study of this series of reactions to establish the definite conditions of formation of the formate and acetate of chlorodimethyl ether, to establish their identity, to determine their physical properties and to extend our study to the propionate and the butyrate, neither of which apparently had ever been made.

Preparation of Chlorodimethyl Ether.—There are four methods recognized in the literature for making this substance. The first, and most generally used up to the time that Wedekind[6] began his study of the compounds in 1903, is known as Henry's method and consists in passing hydrogen chloride into a mixture of formaldehyde and the alcohol whose derivative it is desired to obtain. The second method[7] is of more theoretical interest than of practical value. Ether is treated with chlorine in presence of diffused sunlight. Wedekind, in his method, suggests the use

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[1] *Ann.*, **334**, 1, 49 (1904).

[2] Ger. 137,585, Feb. 26, 1902.

[3] *Ber.*, **36**, 376 (1903).

[4] *Gaz. chim. ital.*, **27**, II, 297 (1897).

[5] *Ber.*, **26**, 1383 (1893).

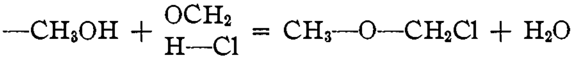
[6] *Loc. cit.*

[7] Friedel, *Compt. rend.*, **84**, 247 (1877).

of paraformaldehyde, triturating it with the molecular amount of alcohol saturated with hydrogen chloride. Zinc chloride is sometimes used as a condensing agent. The reaction is completed by distn. on a water bath with a reflux condenser. A yield of 50 to 60% is claimed. The fourth method[1] is essentially a modification of that of Wedekind. It consists in passing thoroughly dried hydrogen chloride into alcohol and paraformaldehyde. The yield is recorded as 85 to 95%.

Gautier,[2] in 1909, when studying the action of chloromethyl ethers on metallic cyanide, used the method of Henry. This was the method which we adopted for preparing the ether for our experimental work.

Hydrogen chloride, from hydrochloric acid, sp. gr. 1.19, and sulfuric acid, after passing through calcium chloride tubes and a sulfuricacid washer was bubbled into a molecular mixture of methyl alcohol and formalin contained in a one-liter Drexel washing bottle (tall form) surrounded by a freezing mixture of salt and ice. It was found that 270 g. of 40% formaldehyde, containing 8–10% of methyl alcohol, and 80 g. of pure methyl alcohol gave good results. The equation for the reaction may be stated semi-structurally as follows:



$$—CH_3OH + \begin{matrix} OCH_2 \\ H—Cl \end{matrix} = CH_3—O—CH_2Cl + H_2O$$

The following data represents the average results of six experiments:

Per cent. increase in weight	74
Per cent. increase in volume	49
Per cent. yield, crude	63
Per cent. yield, pure	43
Average run	9 hours

The saturation of the methyl alcohol and formalin with hydrogen chloride occupies a considerable part of the time. But when once accomplished the layer containing the chloro ether separates out on top of the reaction mixture and the process goes smoothly to the end. The upper layer shows no tendency to decompose or revert, even when allowed to stand for several days. The formation of a red color in the reaction mixture is mentioned by several observers. We carried forward a series of experiments which indicated that this is due to acetone present as an impurity in the wood alcohol. To make our ether we finally used acetone-free methyl alcohol.

In purifying the crude ether the upper layer was removed and a stream of dry carbon dioxide or dry air was passed through it to take out excess of hydrogen chloride. It was then dried over fused calcium chloride and distilled. The fraction coming over between 55° and 65° was redistilled and the liquid boiling from 57° to 62° was saved. A final fraction was col-

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[1] Ger. 135,310, Aug. 31, 1901.

[2] *Ann. chim. phys.*, 16, 289–358 (1909).

lected between 58° and 60°, and used in our later experiments. When heated to 70° and above some blackening is in evidence in the flask.

The chlorodimethyl ether boils at 59–60°. Analysis showed it contained 29.75% carbon, and 6.48% hydrogen (theoretical, 29.87 and 6.26%). The ether is unstable in the presence of moisture, breaking down into the aldehyde, alcohol and hydrogen chloride. For this reason we found it necessary when distilling the ether, to use dry vessels and to protect the air with calcium chloride tubes. During distillation a deposit of paraformaldehyde was formed in the condenser, and we were able to confirm the observation of Wedekind that this substance is formed only when relatively small amounts of water are present, formaldehyde being produced with larger quantities of water.

In another paper we shall give more details concerning this and other chloro ethers.

Methoxymethyl Formate.—Chlorodimethyl ether was added to the theoretical amount of lead formate in a medium-sized balloon flask connected to a reflux condenser. The formate had been dried for three days over sulfuric acid in a vacuum desiccator. When the formate and ether were brought together a considerable amount of heat was generated, the reaction being

$$2CH_2Cl\text{-}o\text{-}CH_3 + (HCOO)_2Pb = 2HCOOCH_2\text{-}o\text{-}CH_3 + PbCl_2.$$

Then the flask and contents were heated on a water bath for several hours. During this period some decomposition occurs, as is shown by the formation paraformaldehyde in the condenser. In spite of this, on subsequent distillation, a clear cut, regular fraction was obtained, coming over between 101° and 104°, and a second fractionation gave 102–103°. We found that the lead salt produced much better results than the formates of barium and calcium. The yield was 20%.

The formate of chlorodimethyl ether, or methoxymethyl formate, as it may be called, reacts with water in the following way:

$$HCOO - CH_2 - OCH_3 + HOH = HCOOH + HCHO + CH_3OH$$

It burns with a bluish flame.

The product which we prepared, boils at 102–103° and has a molecular weight of 89.2 (theoretical, 90). It is clear liquid with a sharp, slightly ethereal odor. Density: $D_{0°}$ 1.1030, $D_{18°}$ 1.0866, $D_{25°}$ 1.0777.

Methoxymethyl Acetate.—This compound was made in much the same manner as the formate. Lead and zinc acetates did not give us good results, but with fused potassium and sodium acetates a very satisfactory and definite product was obtained. The reaction mixture connected with the reflux condenser was heated for eight hours at a temperature of 120°. A first fraction coming over between 115–119° was separated. The yield was 35–40%. The increase of the acetate over the formate we assume to be due to the use of the fused salt as well as the greater stability of the acetate. The acetate is not as inflammable as the formate, but it too burns with a purplish flame when ignited.

The boiling point is 117–118°. The calculated molecular weight is 104, that found 103. Density: D_{0° 1.0562, D_{18° 1.0358, D_{25° 1.0280.

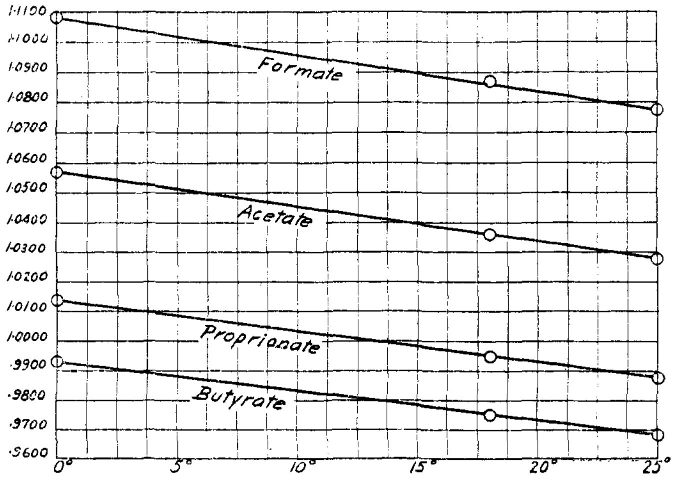
Methoxymethyl Propionate.—There is no reference to methoxymethyl propionate in the literature that we could find. We used fused lead propionate, the temperature being kept at or below 120°. When the propionate and ether are mixed there is a great deal of heat given off, the reaction being more vigorous than in the two preceding cases. In fact the reaction is completed almost at once, and it is not necessary to heat for a long time on the water bath. The yield was 60–65%. No paraformaldehyde was produced in the condenser. The methoxymethyl propionate does not burn very readily, nor does it decompose nearly so easily with water as the previous products. It possesses, more than the other two, an ethereal odor, but still somewhat pungent.

The boiling point is 133°, the molecular weight 116.7 (the theoretical being 118). Density: D_{0° 1.0137, D_{18° 0.9945, D_{25° 0.9872.

Methoxymethyl butyrate was made from fused sodium butyrate. The yield was 75%. When preparing the butyrate, as well as other compounds, we obtained better products by using somewhat more than the theoretical amounts of the organic salts. The butyrate is very difficultly inflammable and decomposes with water. It has a marked ethereal odor.

It boils at 151–152°. The molecular weight was 130.7 (theoretical 132). Density: D_{0° 0.9929, D_{18° 0.9747, D_{25° 0.9678.

It will be noted that the stability of the compounds becomes greater as the —CH_2— groups are added. The introduction of a methylene



group produces a rise in boiling point of about 16°. The effect of the density is illustrated graphically in the accompanying figure. The decrease in the density of the methoxymethyl salts with rising molecular weight is analogous to the behavior of the chloro ethers, investigated by Favre.[1] All of the liquids freeze below —79°. While the two lower compounds are very unstable in the presence of water, none of the liquids fume in air.

Two of the present authors are engaged on further studies of these and similar reactions. We desire to thank E. Emmet Reid for important suggestions.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC ANALYSIS OF THE UNIVERSITY OF ILLINOIS.]

THE QUALITATIVE IDENTIFICATION OF THE DRUGS CONTAINING EMODIN.[2]

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Cascara, Rumex, Rhubarb, Frangula, Senna, and Aloes are the best known members of the group of drugs which are supposed to owe their medicinal properties to the fact that they all contain some derivative of a methyl anthraquinone, such as emodin, chrysophanic acid, or their homologs or isomers, or glucosides yielding these compounds on hydrolysis. A summary of the most authentic analyses of these drugs shows the following compositions:

Alexandrian Senna.[3]—The anthraquinone derivatives are rhein, aloe-emodin and their glucosides. In addition to these are the other substances commonly found in plant drugs, such as sugars, alcohols, acids, and resins.

Cascara Sagrada[4] contains emodin and iso-emodin, but no glucosides of emodin or chrysophanic acid. In addition to the other common substances are found syringic acid and the alcohol rhamnol.

Rumex Ecklonianus.[5]—This drug contains, in the overground portion of the plant, emodin, emodin-mono-methyl ether, and chrysophanic acid.

Rumex Crispus.[6]—No recent analysis of this drug could be found.

Rhubarb.[7]—Contains rhein, emodin, emodin-mono-methyl-ether, aloe-emodin, chrysophanic acid and their glucosides, as well as a new anthraquinone, rheinolic acid.

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[1] Favre, *Bull. soc. chim.*, [3] 11, 879 (1894).

[2] Presented in part at the Urbana meeting of the American Chemical Society.

[3] Tutin; *J. Chem. Soc.*, **103**, 2006 (1913).

[4] Jowett, *Proc. Am. Pharm. Assoc.*, **52**, 228 (1904).

[5] Tutin and Clewer, *J. Chem. Soc.*, **97**, 1 (1910).

[6] The authors are now engaged in a study of its proximate composition.

[7] Tutin and Clewer, *J. Chem. Soc.*, **99**, 946 (1911).