

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

**METHYLETHYL SULFATE AS AN ALKYLATING AGENT**

BY FLOYD K. THAYER

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The secondary, or neutral, esters of sulfuric acid have long been known to possess the power of alkylation but, on account of difficulties encountered in the preparation, dimethyl sulfate and, more recently, diethyl sulfate have been the only ones used to any extent as alkylating agents.

In the use of dimethyl and diethyl sulfates as alkylating agents, it is well known that not only does one alkyl group split off, leaving a primary sulfate but, in most cases, a large percentage of the second alkyl group enters into the reaction. Thus an interesting phase in the study of this type of reaction presented itself in the investigation of the alkylating properties of mixed alkyl sulfates, particularly methylethyl sulfate, especially as regards the comparative alkylating power of the two alkyl groups. This paper deals with the preparation of methylethyl sulfate and the results obtained when it was used to alkylate phenol.

Behrend<sup>1</sup> claimed to have prepared methylethyl sulfate in two ways: by the action of methyl alcohol upon the ethyl esters of chlorosulfonic acid ( $C_2H_5OSO_2Cl + CH_3OH \rightarrow C_2H_5OSO_2OCH_3 + HCl$ ), and the reverse process of ethyl alcohol upon the methyl ester of chlorosulfonic acid. Behrend stated that, when this methylethyl sulfate was treated with water, the methyl group was hydrolyzed according to the equation:  $C_2H_5OSO_2OCH_3 + H_2O \rightarrow C_2H_5OSO_2OH + CH_3OH$ . Thus it was to be concluded from Behrend's work that the methyl group was the most active and, therefore, would be the group with the most pronounced alkylating property.

Claesson,<sup>2</sup> however, has shown Behrend's work to be unreliable. Both Bushong<sup>3</sup> and the writer attempting to repeat Behrend's preparation of mixed alkyl sulfates, have arrived at the same conclusion. Bushong, and not Behrend, was actually the first to prepare mixed alkyl sulfates. However, he did not prepare methylethyl sulfate, but confined his work to the synthesis of ethyl-*iso*-amyl, ethyl-*iso*butyl, and ethyl-*iso*propyl sulfates. Furthermore, in no case did he test any of his secondary sulfates as alkylating agents.

In the determination of the comparative alkylating properties possessed by the methyl and ethyl groups, standard conditions were necessary.

As a standard, the following method gave a close check in two trial runs in which dimethyl sulfate was used. One molecular equivalent of phenol was dissolved in 10% sodium hydroxide solution in which the molar

<sup>1</sup> Behrend, *J. prakt. Chem.*, [2] 15, 23 (1877).

<sup>2</sup> Claesson, *ibid.*, [2] 19, 231 (1879).

<sup>3</sup> Bushong, *Am. Chem. J.*, 30, 316 (1903).

strength of the sodium hydroxide was  $\frac{1}{10}$  greater than that of the phenol. This solution was treated with 1 molecular equivalent of dimethyl sulfate. The amount of pure vacuum-distilled anisole obtained by this method in two runs was 73.8% and 74.7% of that calculated.

The same procedure was followed when the methylethyl sulfate was allowed to react with phenol. The yield of anisole was found to be 56.7% of that calculated, that is, the anisole formed was 56.7% of that which would have been formed if all the methyl group had reacted. The corresponding yield of phenetole was 13.4%. This means that of the total amount of alkylation performed upon the 1 molecular equivalent of phenol, the methyl group was responsible for 80.2% and the ethyl group for 19.8%.

No attempt was made to use more than 1 equivalent of phenol, for in that case not only would the most reactive group alkylate, but there would also be an opportunity for the less reactive group to break off. Furthermore, no effort was made to find the most optimum conditions for the reaction; it was thought to be sufficient that the method checked within experimental error. The comparative alkylating power, not the absolute, was sought.

### Experimental Part

**Ethyl Ester of Chlorosulfonic Acid.**—The method of Willcox<sup>4</sup> was used; yield, 71%; b. p., 92–95° (100 mm.).

**Preparation of Methylethyl Sulfate.**—Bushong's method of preparing mixed alkyl sulfates consisted of the addition of 1 molecular equivalent of the ethyl ester of chlorosulfonic acid to 1.5 or 2 equivalents of the sodium alcoholate suspended in ligroin or ether. He states, "When absolute ether and 1.5 mols. of the alcoholate are used, an almost clear solution results after some standing." The writer has been unable, in any of his various experiments, to obtain a clear solution. Furthermore, the preparation of methylethyl sulfate by this method necessitated refluxing the reaction mixture for a period of 24 hours. Such a reaction might be expected to offer excellent opportunities for side products, and this was found to be the case. Necessarily then, the yield of mixed alkyl sulfate was low.

To a dry ether suspension of 26 g. of sodium methylate (free from alcohol) 90 g. (1.3 equivalents) of ethyl chlorosulfonic acid was added slowly while the liquid was stirred. After the addition was complete the reaction mixture was refluxed on the water-bath for 24 hours, filtered from the salt and the ether removed under diminished pressure. The remaining liquid, methylethyl sulfate, boiled at 198–200° (742 mm.); yield, 13.2 g., or 19.7%.

*Analysis.* Subs., 0.4323: BaSO<sub>4</sub> (Carius), 0.7128. Calc. for C<sub>8</sub>H<sub>8</sub>O<sub>4</sub>S: S, 22.85. Found: 22.60.

**Alkylation with Dimethyl Sulfate.**—A mixture of 36.6 g. of phenol with 19.6 g. (1.1 molecular equivalents) of sodium hydroxide and 176 cc. of water was cooled with ice and stirred while 50 g. (1 equivalent) of dimethyl sulfate was added drop by drop. The stirring was continued for five minutes after all the dimethyl sulfate had been added. The reaction mixture was refluxed for 15 minutes; by this time it had separated into definite layers of anisole and aqueous solution. After the mixture had cooled, the anisole

<sup>4</sup> Willcox, *Am. Chem. J.*, **32**, 446 (1904).

was separated and dried over a little anhydrous calcium chloride. The product boiling at 45–55° (11 mm.) weighed 31 g.

The experiment was repeated using half quantities. The anisole thus obtained amounted to 15.7 g.

**Alkylation with Methyleneethyl Sulfate.**—The same procedure was followed as described for dimethyl sulfate; 27.3 g. (1 molecular equivalent) of methyleneethyl sulfate was used; yield of anisole 11.4 g., of phenetole 3.2 g.

### Acknowledgment

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### Summary

1. The new compound, methyleneethyl sulfate, was prepared.
2. Phenol was alkylated with one molecular equivalent of methyleneethyl sulfate under conditions standardized by the use of dimethyl sulfate. Of the total amount of alkylation performed upon the phenol by methyleneethyl sulfate, the methyl group was responsible for 80.2% and the ethyl group for only 19.8%.

URBANA, ILLINOIS

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[CONTRIBUTION FROM THE CARBOHYDRATE LABORATORY, BUREAU OF CHEMISTRY,  
UNITED STATES DEPARTMENT OF AGRICULTURE]

## THREE ISOMERIC CRYSTALLINE TETRA-ACETYL-METHYL-*d*-MANNOSIDES

By J. K. DALE

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The generally accepted butylene oxide structure accounts for the existence of two isomeric forms of each of the mutarotating sugars and for two isomeric forms of many of their derivatives. Evidence that more than two isomers of these sugars and their derivatives may exist was first brought out by Fischer<sup>1</sup> who obtained in sirup form a third methyl-*d*-glucoside having properties markedly different from those of the previously known alpha and beta forms. Shortly afterwards, Hudson<sup>2</sup> crystallized a third form of *d*-galactose penta-acetate and later isolated a fourth crystalline isomer. Irvine<sup>3</sup> and his co-workers have also produced evidence of the existence of more than two isomeric forms of some of the mutarotating sugars, while Fischer, Bergmann and Rabe<sup>4</sup> have prepared three crystalline isomeric triacetyl-methyl-*l*-rhamnosides.

This article describes the preparation and properties of three crystalline tetra-acetyl-methyl-*d*-mannosides. Direct acetylation of methyl-*d*-man-

<sup>1</sup> Fischer, *Ber.*, **47**, 1980 (1914).

<sup>2</sup> Hudson, *THIS JOURNAL*, **37**, 1591 (1915); **38**, 1223 (1916).

<sup>3</sup> Irvine and others, *J. Chem. Soc.*, **107**, 524 (1915); **109**, 1305 (1916).

<sup>4</sup> Fischer, Bergmann and Rabe, *Ber.*, **53**, 2362 (1920).