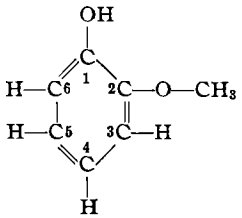
POTASSIUM GUAIACOL SULPHONATE.*

BY A. H. CLARK AND ERNST KIRCH.

For several years potassium guaiacol sulphonate has been used as a medicament in the treatment of those conditions in which guaiacol is indicated. Since it is a very stable compound, as all aromatic sulphonates are, its use may be looked upon as irrational but it is popularly believed to be absorbed as an entire molecule and in this way acts as does guaiacol. Be this as it may it is very widely used, especially as a syrup, and its manufacture and sale is a commercial enterprise of considerable importance.

There are several guaiacol sulphonic acids and their salts possible from a theoretical standpoint and some of these have been described. Guaiacol, the basic substance, has the following structure:



If the carbon atoms of the ring are numbered as above it is seen that four guaiacol sulphonic acids are possible, namely the 1,2,3, the 1,2,4, the 1,2,5 and the 1,2,6. From each one of these acids, as well as by replacement of the hydrogen in the OH group, or in both ways at once, salts may be formed. Several guaiacol sulphonates are thus possible. The only ones of importance in which we are interested at the present time are those in which the metal enters the sulphonic acid group since the presence of the potassium in the OH group is incidental only.

Much confusion in the nomenclature of these salts is occasioned by different writers using such terms as ortho, meta, para, viscinal, alpha, etc., to indicate the position of the three substituents in the benzene ring. It is not always clear whether the OH or the OCH_3 group is the basic one used and it is evident that two viscinal compounds are possible. To avoid all confusion in the following discussion the system of numbering as given above will be used throughout and even the terms used by others will be translated into this system when it is possible to do so.

The questions that prompted this investigation are: Is there any difference in therapeutic activity between the four possible salts? If so, which one is the most active? If any one is more active than the others how may it be distinguished from the others? What is the product commonly sold? When it is considered that many pharmaceutical houses market potassium guaiacol sulphonate without any statement as to what it is, the importance of a correct answer to these questions is obvious.

Search of the available literature reveals no records of painstaking pharmacological work on this substance. From its very nature it might be assumed to liberate guaiacol with difficulty and therefore have no value unless it is absorbed as

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an entire molecule. Fränkel (1) states that the 1,2,4 compound has no value while the 1,2,6 has. May (2) states that the 1,2,3 compound is therapeutically useful and that the 1,2,4 has no value. Barrowcliff and Carr (3) state that it is important the salt should be free from the 1,2,4 compound. Fourneau (4) states that Thiocol is the 1,2,6 compound. Rosenthaler (5) states that Thiocol is 1,2,6 and that the 1,2,4 is not to be employed. Evers (6) states that potassium guaiacol sulphonate is the salt of the 1,2,5 acid.

In this connection some value may be attached to the fact that the following authorities recognize the 1,2,6 compound, specifically mentioning it in their descriptions which would indicate preference over the others. New and Nonofficial Remedies of the A. M. A., all editions from 1918 to 1934, inclusive; Svenska Farmakopen, 1925; Pharmacopœa Hungarica, IV, 1934; British Pharmaceutical Codex, 1934; Deutsches Arzneibuch, Prior to 1926; Merck's Index, IV, 1930.

Other authorities described it as follows: Pharmacopœa Helvetica, V, 1933, as a mixture of 1,2,4 and 1,2,5; Deutsches Arzneibuch 1926 as a mixture of 1,2,4 and 1,2,5; Pharmacopea Jugoslavica 1933 as 1,2,5.

The first to give attention to guaiacol sulphonic acid or potassium guaiacol sulphonate seems to have been Tiemann and Koppe (7) but Barell (8) was the first to make any study of its structure. He thought that he had made the 1,2,6 acid. This conclusion seems to be incorrect in the light of later and very thorough work which is ably presented by Paul (9). The latter showed that by sulphonating guaiacol below 100° C. a mixture of the 1,2,4 and 1,2,5 acids is formed. Rising (10) studied the subject about the same time and published the results of his work a little later. He concludes that the 1,2,4 and the 1,2,5 acids are readily prepared at temperatures below 100° C., most readily at 70° C. If the temperature is 135–140° C. he claimed to have prepared a so-called viscinal acid, either the 1,2,3 or the 1,2,6. These various acids were studied, their potassium salts described and other facts recorded. He concluded that the marketed products at that time were mixtures of the 1,2,4, the 1,2,5 and some of the basic salt, that is potassium replacing the hydrogen in the OH group.

Paul (11) published a second paper in which he disagreed with some of Rising's conclusions, holding that the latter's viscinal compound, the 1,2,3 or 1,2,6 was in reality $C_6H_3(OH)(OH)HSO_3$ 1,2,4 and offers evidence to support this stand. It is significant that Rising did not publish any comment on this criticism. At this point the matter rested for about twenty years until Rupp and Brixen (12) published the results of much work done on these products and also pharmaceutical preparations made from them.

From these sources the answers to the last two questions asked in the beginning of this discussion are obtained. With the exception of Barell's work the conclusion is that the products marketed up to 1926 were mixtures of the 1,2,4 and the 1,2,5 compounds with small varying amounts of the basic one. No investigator has shown that any marketed product consisted, even in a small degree of the 1,2,6 compound and it seems certain that it never has been made. We have examined samples of potassium guaiacol sulphonate from seven different sources in addition to Thiocol and every one of them is substantially the same in every way and when examined by the methods used by the authors referred to above are found to be a mixture of the 1,2,4 and 1,2,5 salts.

The tests, data, etc., upon which this conclusion is based are summarized in the following statements.

Physically all samples were about the same. Colorless crystalline powders, odorless, of a faintly bitter taste, and a neutral or slightly alkaline reaction to litmus. Marked alkalinity indicates basic character, *i. e.*, some of the H in the OH group replaced.

The melting points of the free acids obtained from samples prepared directly from guaiacol were 96–97° C. for the 1,2,4 and 106.5–107.5° C. for the 1,2,5. The same acids prepared from Thiocol gave 96.5–97.3° C. and 106.5–107.5° C. and from one commercial sample, acids isolated gave 96.5–97.5° C. and 106–107.5° C. The figures given by Rising (10) are 97–98° C. and 106–108° C. Since all other samples were alike in other respects no further melting point determinations were made.

Every sample gave dinitroguaiacol the melting point of which varied between 121.5° and 122° C., indicating according to Rupp and Brixen (12) the presence of the 1,2,4 compound. The figure given by Mulliken (13) for this compound is 122° C. The following four reactions are the same as used by Rupp and Brixen.

Ferric chloride gave a blue coloration with every one of our samples.

Lead acetate precipitates the 1,2,4 acid but not the 1,2,5 and all samples behaved alike with this reagent.

Lead subacetate precipitates both the 1,2,4 and the 1,2,5 acids and with those samples on which this test was tried precipitates were obtained.

Ammonia water and calcium chloride precipitate with the 1,2,4 acid but not with the 1,2,5. This was the case with those samples on which the test was used.

Upon coupling with diazobenzene as directed by Rising both the 1,2,4 and the 1,2,5 compounds give an orange-red coloration but no precipitate. This coloration was given by all our samples.

The solubility in water is of some interest since the 1,2,5 salt is much more soluble than the 1,2,4. All our samples were freely soluble and all about alike. From a careful observation all samples examined contained about 75% of the 1,2,4 and 25% 1,2,5.

Rising claimed that his viscinal compound, the 1,2,6 or 1,2,3 as he stated it to be, gave a green color with ferric chloride, a purple color with lead acetate, a precipitate only after standing with lead subacetate and brown flakes with diazobenzene. Since no sample examined by us gave any of these reactions, not one of them contained what Rising thought to be the 1,2,6 compound.

CONCLUSIONS.

This study has brought out the following facts about potassium guaiacol sulphonate.

1. That the evidence supporting the belief that the 1,2,6 compound is the most valuable from a therapeutic standpoint or that the 1,2,4 is valueless or harmful, is very slight and practically worthless.
2. That the 1,2,6 compound never has been made.
3. That all market products are alike, eight of them having been examined by us.
4. That since the 1,2,6 compound does not exist and the market products are all alike no tests can at present be suggested to distinguish one product from another

unless some manufacturer begins to separate the 1,2,4 from the 1,2,5 and markets a single salt in place of the mixture or some one actually makes the 1,2,6 compound.

5. That the proportion of the 1,2,4 to the 1,2,5 is approximately 3 to 1.

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A COMPARATIVE STUDY OF ENTERIC COATINGS.[1]

BY F. S. BUKEY AND PHYLLIS RHODES.[2,3]

The authors in a previous study of enteric coatings found a wide variation in the efficiency of the coating materials. It was, therefore, decided to test various types of commercial coatings. Several of the pharmaceutical manufacturers agreed to coöperate in this study by applying their enteric coatings on tablets of barium sulphate.

Five different enteric coatings were submitted by the manufacturers for this study. Among these types were two of keratin, one salol-shellac, one shellac and one composed of a mixture of salol and resins. In every case the products submitted were finished and in external appearance resembled any sugar-coated tablet. The uncoated tablets measured 10.5 mm. in diameter and 4.8 mm. in thickness. In addition to the tablets, one manufacturer supplied enteric and sugar-coated No. 1 capsules filled with barium sulphate.

The subjects for these experiments were picked from the student body and in every case normal individuals in apparent good health. The X-ray was used to determine the exact point of disintegration. In general, the following procedure was used in making this study. Each subject was given a certain number of tablets followed at once with a glass of water containing a teaspoonful of Bari-o-meal. The Bari-o-meal was sufficient to outline the stomach, but did not produce a density great enough to mask the tablets. The first radiograph was usually taken after 30 minutes and others followed at desired intervals until disintegration occurred.

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