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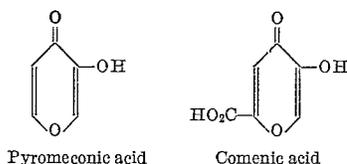
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**PREPARATION OF COMENIC AND PYRO-  
 MECONIC ACIDS**

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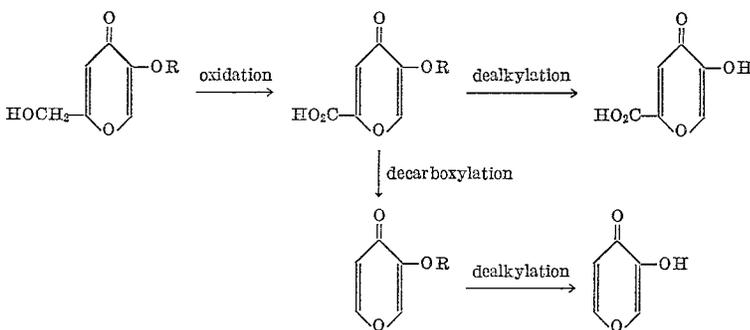
This invention relates to a new and advantageous method for making certain hydroxypyranones and it is particularly concerned with the preparation of comenic and pyromeconic acids.

Substituted pyranones such as those mentioned are useful intermediates for compounds having pharmacological value. Comenic acid and pyromeconic acid are hydroxy-4-pyranones of the structures shown.



These compounds have previously been available only as by-products of opium processing or as the products in very low yields of difficult and complex syntheses.

We have now found that both the above compounds specifically, and similar hydroxypyranones in general, can be obtained in relatively good yields as the products of a straightforward system of synthesis utilizing as a starting material the commercially available kojic acid, this compound being the 5-hydroxymethyl derivative of pyromeconic acid. The system of synthesis is shown schematically by the following diagram, starting with the monoalkyl ether of kojic acid which is made by the alkylation of kojic acid by any of several conventional procedures.



In the above diagram, R represents a lower alkyl hydrocarbon radical. Although general methods for accomplishing all the above steps are broadly known, we have found specific means which are novel in their particular application in each case and which yield unexpectedly superior results when so used. As a result, the combinations of steps shown offer for the first time a practical method whereby each of the two products is obtainable in a commercially acceptable yield.

Referring now to the steps of the overall process in turn, the 5-methyl ether of kojic acid has been oxidized to the corresponding ether of comenic acid in the past by such methods as reaction with potassium permanganate or nitric acid, and oxidation with atmospheric oxygen in the presence of platinum catalyst. The yields of comenic acid methyl ether were uniformly poor, being about 40 percent based on material converted. We have found that by substituting a palladium catalyst for the platinum previously used in the air oxidation, the yield of comenic acid ether is increased to unexpected proportions, thereby

converting a laboratory process to one which is commercially feasible. The general conditions for the oxidation are those under which the prior art platinum-catalyzed oxidation was run as described by Heyns et al., Chem. Ber, 87, 13 (1954). For example, the oxidation is carried out in inert solvent suspension, water being the most practical solvent, and the suspension is maintained under approximately neutral or slightly acidic conditions, suitably by appropriate addition to the mixture of a moderately or weakly basic water-soluble compound such as sodium carbonate, potassium bicarbonate or the like. The operable pH range is about 4-8. Under more strongly acidic conditions, the oxidation does not take place, and at higher pH, the pyrone ring becomes unstable and breaks down. A suitable temperature for the reaction is in the range 50°-100° C. Higher or lower temperatures may be employed but are usually not desirable. The proportions of water and of catalyst to the kojic acid ether are those to make convenient reaction conditions. The catalyst is preferably finely divided palladium supported on an inert carrier such as carbon or alumina. For the commonly used 5 percent palladium on carbon, a weight ratio of three or four parts of ether to one part of supported catalyst has been found suitable. Separation of the oxidized product from the aqueous solution obtained is by conventional methods.

Decarboxylation of the comenic acid ether product to the corresponding ether of pyromeconic acid has been found to be easily accomplished merely by heating at about 200°-250° C., preferably at 220°-230° C. Prior art methods for similar reactions include the decarboxylation of both meconic acid and comenic acid to pyromeconic acid by heating in the presence of copper. For example, Garkusha, J. Gen. Chem., U.S.S.R., 16, 2025 (1946), obtained a 48 percent yield of pyromeconic acid by heating equal weights of comenic acid and copper powder. Surprisingly, the use of decarboxylation cata-

lysts such as copper or copper in the presence of quinoline turned out to be disadvantageous in the decarboxylation of alkyl ethers of comenic acid, a very low yield or no yield at all of the desired product being thereby obtained. The decarboxylation is best carried out in inert solvent suspension to avoid excessive decomposition through overheating. Suitable media include diphenyl ether, similar aromatic hydrocarbon ethers, and high-boiling hydrocarbons such as cetane or diphenyl.

Ethers as a class have been cleaved to form an alcohol by heating in contact with a variety of acidic reagents, including acids such as hydrobromic acid, hydriodic acid and sulfuric acid, and acidic salts such as aluminum chloride, zinc chloride, stannic chloride and boron trifluoride. Ordinarily, all of such reagents will work to some extent when applied to a particular ether although one or more may give somewhat better results than the others, depending upon the ether in question. However, in the present case, all but one of the conventional reagents as cited above either fail to produce any ether cleavage or cause