NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XXIX. A Note on the Synthesis of 3-Methyl-Gallic and Myristicic Acids

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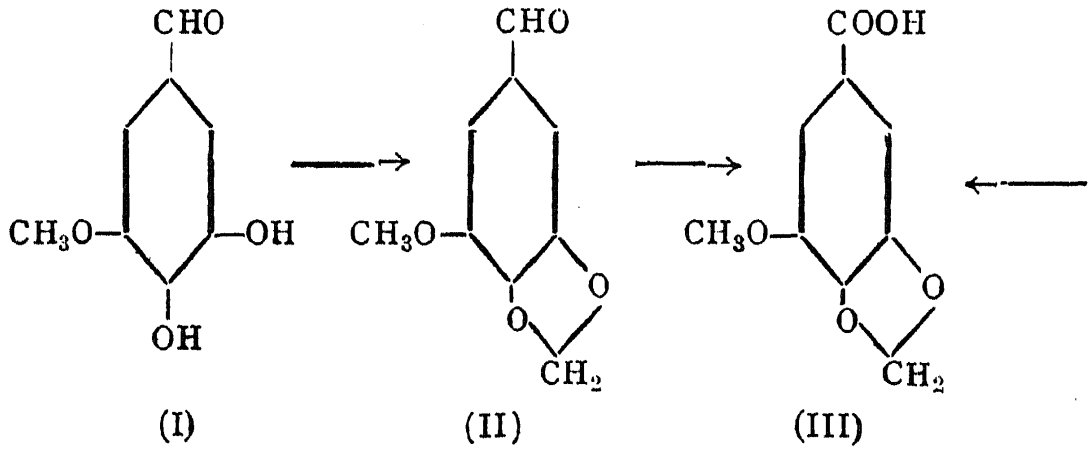
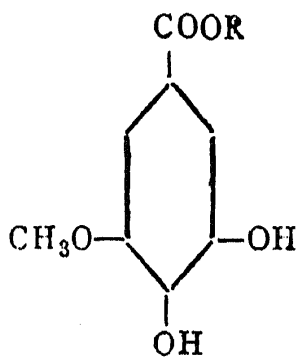
MYRISTICIC ACID (III) was first synthesised by Baker[1] by the methylenation of 3-methyl-gallic aldehyde (I) and subsequent oxidation. An improved method of methylenation was used by Rao and Seshadri[2] and this considerably increased the yields. An alternative method would be to methylenate 3-methyl gallic acid (IV, R=H) itself. This has now been satisfactorily worked out. The acid is first esterified and the crude ester (IV, $R=C_2H_5$) methylenated with methylene iodide and potassium carbonate in dry acetone medium and the product subsequently saponified. A yield of about 60% of myristicic acid is obtained.



(I) (II) (III)

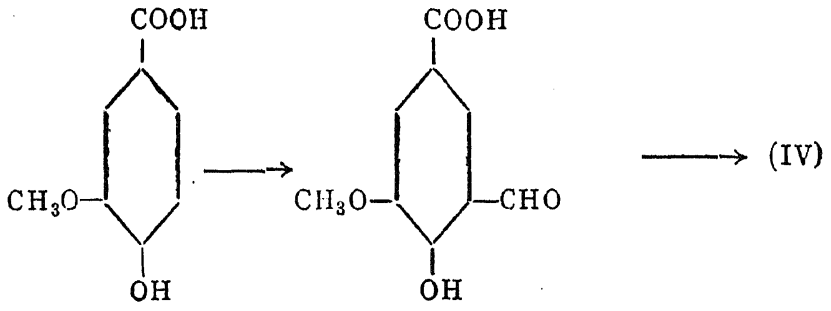


(IV)

3-Methyl-gallic acid (IV, R=H) required for this purpose was first made by Vogl[3] starting from vanillin and passing through a number of stages. The melting point was recorded as 200° which is too low. Subsequently Fischer[4] made it from gallic acid, first making the carbonato

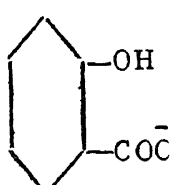
derivative using phosgene, subsequently methylating it and hydrolysing the carbonato group. Later Bradley, Robinson and Schwarzenbach[5] modified this procedure employing dichlorodiphenylmethane instead of phosgene. They also pointed out that the correct melting point of this substance is 220° and the melting point 131–132° given by Shriner and McCutchan[6] was due to an error owing to the mistaking of 3-methyl gallaldehyde for this acid.

The above 3-methyl-gallic acid (IV, R=H) has now been made by adopting the two-stage method of nuclear oxidation, analogous in procedure to the recent synthesis of hydroxy eugenol.[7] Vanillic acid (V) is used for this purpose. By the action of hexamine an aldehyde group is introduced in the 5-position (VI) which undergoes smooth oxidation with hydrogen peroxide to give a good yield of the required acid (IV). Its identity is established not only from its properties, but also by methylation to trimethyl gallic acid.



(V) (VI)

The above experiments constitute a typical example for the suitability of this method of nuclear oxidation even when carboxyl groups are present. Such groups, present para or ortho to phenolic hydroxyl groups, have been found in test experiments to be unaffected in Dakin's reaction. A discussion of this reaction has been given in a recent publication.[8] The non-reactivity of the carboxylic acids could be attributed to the lack of development of the adequate degree of positive charge on the carbon atom belonging to the carboxyl group. In alkaline medium the negative charge on the carboxylate ion (VII) may be expected to produce this adverse effect and it will be absent in the corresponding aldehydes and ketones.



Experimental

Vanillic acid-5-aldehyde (VI)

Vanillic acid (3 g.) and hexamine (12 g.) were dissolved in hot glacial acetic acid (22·5 c.c.) and the clear yellow solution was heated on a boiling water-bath for six hours. Boiling hydrochloric acid (1 : 1, 30 c.c.) was then added and the heating continued for half an hour more. The yellow crystals of vanillic acid-5-aldehyde, obtained on cooling the solution, were recrystallised from alcohol to give yellow needles melting at 223–4°. Yield 1 g. It was soluble in sodium carbonate and sodium hydroxide solutions. It gave a pink colour with alcoholic ferric chloride. (Found: C, 54·8; H, 4·3; $C_9H_8O_5$ requires C, 55·1; H, 4·1%.) (Tiemann and Mendelsohn[9] who adopted the Reimer-Tiemann method gave the melting point as 221–2°.)

Oxidation of vanillic acid-5-aldehyde. Preparation of 3-methyl-gallic acid (IV, R=H)

The aldehyde (1 g.) was dissolved in normal alkali (7·8 c.c.) and pyridine (3 c.c.). Hydrogen peroxide (6%, 4 c.c.) was added to the cooled solution drop by drop. It was then left aside for two hours. The solution, after acidifying with hydrochloric acid, was saturated with sodium chloride and extracted with ether and the extract washed with dilute hydrochloric acid. On evaporating the solution, 3-methyl gallic acid was left behind as a brown crystalline solid. It was crystallised from a mixture of ethyl acetate and benzene to give almost colourless needles melting at 221° (decomp.) Yield 0·8 g. It gave a bluish violet colour with alcoholic ferric chloride.

Trimethyl gallic acid

The dihydroxy acid (0·2 g.) was methylated with dimethyl sulphate (0·3 c.c.) and sodium hydroxide (1 N; 5 c.c.). After heating for half an hour on the water-bath the solution was acidified and the crystalline precipitate formed was filtered and recrystallised from hot water when it was obtained in the form of colourless needles melting at 167°. Mixed melting point with an authentic sample of trimethyl gallic acid was not depressed.

Myristicic acid (III)

The dihydroxy acid (IV, R = H) (1·0 g.) was esterified by refluxing with absolute alcohol (3 c.c.) and a few drops of concentrated sulphuric acid for two hours. Water was then added when the ester (IV, $R = C_2H_5$) separated as a pale brown liquid. It was extracted with ether and the ether extract washed with aqueous sodium carbonate and dried over anhydrous

sodium sulphate. The solvent was then distilled off and any traces of alcohol present were removed under reduced pressure.

The dry residue was methylenated by refluxing in anhydrous acetone solution (50 c.c.) with methylene iodide (2 c.c.) and anhydrous potassium carbonate (8 g.) for 12 hours. The solution was then filtered and the solvent distilled off. Any traces of methylene iodide were removed under reduced pressure over a water-bath. The residue was dissolved in ether and the ether solution washed with aqueous sodium hydroxide and then with water. The ether was then removed by distillation and the ester left behind was hydrolysed by refluxing for half an hour with alcoholic potash. The alcohol was then distilled off and the residue treated with dilute hydrochloric acid. The crystalline precipitate thus obtained was filtered and recrystallised from aqueous alcohol when it was obtained in the form of colourless needles melting at 210°. Yield 0·6 g. It gave a yellow colour with concentrated sulphuric acid and an emerald green colour with gallic acid and concentrated sulphuric acid which gradually changed to bluish green. Mixed melting point with an authentic sample of myristicic acid obtained from natural myristicin was not depressed.

Summary

3-Methyl-gallic and myristicic acids have been synthesised by new methods. For this purpose vanillic acid is converted into its 5-aldehyde and oxidised with alkaline hydrogen peroxide to yield 3-methyl-gallic acid. Esterification, methylenation and hydrolysis give rise to a good yield of myristicic acid.

References

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