
The Molecular Structure of Citrinin

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*Studies in the Biochemistry of Micro-organisms.*PART XV.—*The Molecular Structure of Citrinin.*

By FREDERICK PHILIP COYNE, HAROLD RAISTRICK and ROBERT ROBINSON, F.R.S.

The present communication is, in effect, a discussion of the results obtained in the investigation of citrinin, and described in the preceding memoir (Part XIV); these results, combined with some few further observations, appear to afford a key to the constitution of the substance.

In considering this matter, it is convenient to start with the dihydric phenol, $C_9H_{12}O_2$ (I) (p. 290), which was obtained by fusing either of the isomeric products A or B (p. 283) with potassium hydroxide. This dihydric phenol has the composition of a dihydroxypropylbenzene, but the relative position of the hydroxyl groups and the arrangement of the alkyl side-chain or chains is unknown. The colour reaction with ferric chloride is, however, in agreement with the view that the substance is a resorcinol derivative, rather less well in harmony with the catechol hypothesis, and is hardly reconcilable with the assumption of a quinol nucleus. The dimethyl ether of I, $C_9H_{10}(OMe)_2$, (II) (see p. 290) gave, on oxidation with potassium permanganate, an acid, $C_7H_5(OMe)_2CO_2H$ (III), m.p. 142° – 146° C., and another acid, $C_8H_7(OMe)_2CO_2H$ (IV), m.p. 97° – 99° C. (see pp. 292–293), and examination of these substances has made it clear that I is a resorcinol derivative. Fusion of a mixture of III and IV with potassium hydroxide and recovery of the acid formed gave a product showing a typical resorcylic acid ferric chloride reaction, a violet coloration that was remarkably stable. Further, this product, when heated with phthalic anhydride and a trace of sulphuric acid, gave a phthalein which dissolved in aqueous ammonia to a reddish solution, exhibiting an intense green fluorescence. On strongly heating the product of alkali-fusion of the mixture of III and IV and again fusing with potassium hydroxide and isolating the acidic product, a trace of material was obtained, showing, after condensation with phthalic anhydride, a characteristic fluorescein reaction of resorcinol rather than of alkylresorcinol type. There is thus little doubt that I is a resorcinol derivative, and the formation of the acids III and IV can only be explained on the hypothesis that the substance is a propylresorcinol or a methylethylresorcinol—it cannot be a trimethylresorcinol or an isopropylresorcinol.

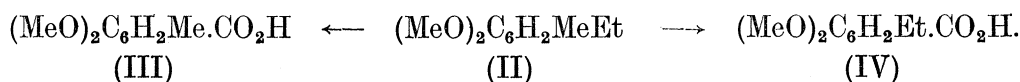
The propylresorcinol possibility is *a priori* unlikely, because it would be necessary to formulate the oxidation of II in accordance with the scheme: $(MeO)_2C_6H_3.CH_2.CH_2.CH_3 \rightarrow (MeO)_2C_6H_3.CH_2.CH_2.CO_2H$ (IV) \rightarrow $(MeO)_2C_6H_3.CH_2.CO_2H$ (III). The only

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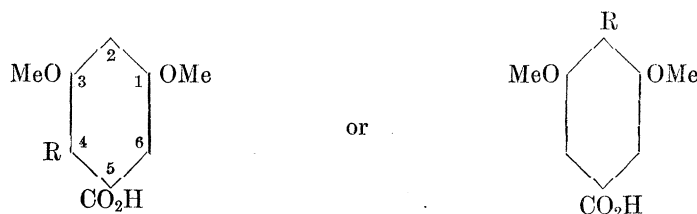
analogies for such graded oxidation of a saturated side-chain in the aromatic series are of very doubtful validity, and it is usually found that permanganate oxidizes fully saturated chains so as to produce derivatives of benzoic acid.

On the view that II is a methylethylresorcinol dimethyl ether, it is possible to represent the formation of III and IV in accordance with the scheme :—



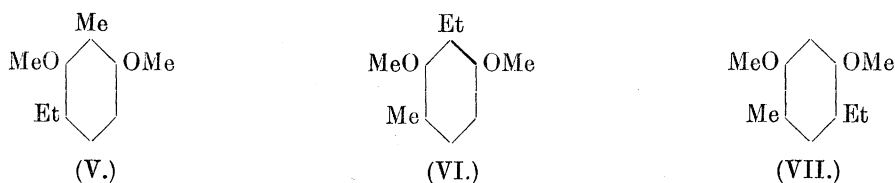
Fortunately, it was possible to show that this scheme does, in fact, represent the degradation, because both III and IV are derivatives of benzoic acid. The direct attachment of the carboxyl group to the nucleus was proved in both cases by applying the CURTIUS reaction to the acids; the amines ultimately obtained were diazotisable and the resulting diazonium salts coupled with β -naphthol to unmistakable azo-compounds. Owing to the small quantities available, the reactions were carried out on a tiny scale, but the results were none the less positive and established this important stage in the argument.

The next point to notice is that neither the methyl nor the ethyl group can be in position 5 in the nucleus, for, if this were so, one of the acids III or IV would be of the form



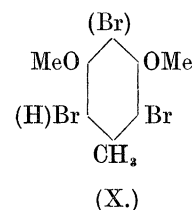
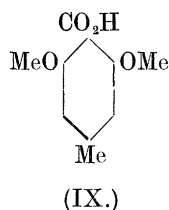
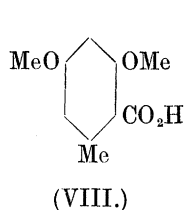
where $R = \text{Me}$ or Et . In either case, one of the acids III or IV would be a 3:5-dimethoxybenzoic acid with a free position *o-p.* to methoxyl, and, when heated with sulphuric acid, an intense colour would be developed owing to the formation of an anthrachryson derivative. However, neither III nor IV exhibits such a colour reaction when heated with sulphuric acid.

It follows that II must have one of the three formulæ V, VI or VII.



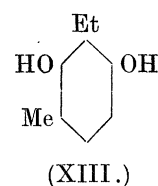
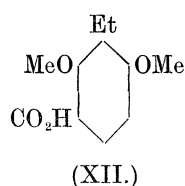
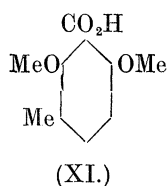
According to formulæ V and VI, the relation of the carboxyl to the methoxyl groups in III and IV will be different, but in VII the relation will be the same and both III and IV would be 2:4-dimethoxybenzoic acids.

In searching for a diagnostic reaction, we were greatly assisted by having in our possession pure specimens of the dimethyl ethers of orsellinic acid (VIII) and of para-orsellinic acid (IX), and a significant divergence in their behaviour was noted when bromine water was added to a cold, dilute solution in aqueous sodium carbonate. This reaction was already known to be capable of distinguishing between somewhat similarly



constituted alkyloxy-benzoic acids (compare JONES and ROBINSON (1917)). Thus, the carboxyl group of veratric acid is displaced by bromine but not that of a methoxy-veratric acid, namely, gallic acid trimethyl ether. The displacement of the carboxyl group occurs, apparently, most easily when methoxyl is situated in the *p*-position to it. VIII gives an immediate precipitate of a neutral di-bromo-derivative (X), whereas IX gave no precipitate under the same conditions.

The substance from VIII crystallised from ethyl alcohol, in which it is sparingly soluble, in colourless prismatic needles, m.p. 168° – 169° C. (Found: Br, 51.2 per cent. $C_9H_{10}O_2Br_2$ requires Br, 51.6 per cent.). It is therefore 2 : 6 (or 2 : 4)-*dibromo-orcinol dimethyl ether*. On testing the acids III and IV in the same way, it was found that no precipitation occurred when bromine water was added to a solution of III in aqueous sodium carbonate; this fact, alone, suggests that III must have the formula XI and excludes VII for the substance II. Clearly, this requires that IV should be represented by the formula XII and should yield a

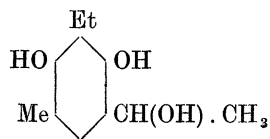


neutral bromo-derivative when bromine is added to its alkaline solution. Actually, this was found to be the case, and the bromo-derivative (probably, 2 : 4-dibromo-6-ethylresorcinol dimethyl ether, but it may also be a mono-bromo-derivative) crystallised from methyl alcohol in colourless needles, but was obtained in such small amount that a fuller description must be reserved.

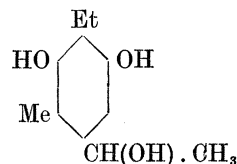
We arrive at the definite conclusion that the dihydric phenol (I) has the constitution XIII, and this is in full agreement with the properties of the substance.

Now, I (XIII) is derived from the products A and B, $C_{11}H_{16}O_3$, by alkali fusion and, from the compositions, the optical activity of product A and chemical analogies (which

exclude attachment of the group, removed by the potash fusion, to the alkyl side-chains), it is only possible to admit one of the formulæ XIV or XV as adequate representations of the constitution of product A (or B).

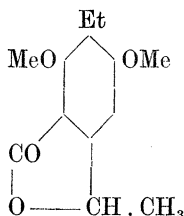


(XIV.)

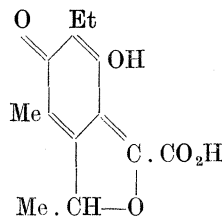


(XV.)

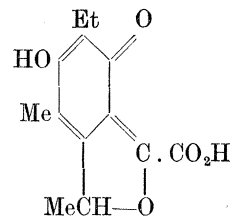
Either of these expressions (XIV or XV) is in harmony with the general character of the substances, $C_{11}H_{16}O_3$, as dihydric phenols containing also an alcoholic hydroxyl group, but XV is to be preferred, (a) because products A and B couple with diazonium salts to azo-compounds and (b) because, on the basis of the formula XV, the lactone obtained on oxidation of the dimethyl ether of product A (see Part XIV, p. 289) can be assigned the constitution XVI. No such natural explanation of the results is possible on the basis of XIV for products A and B.



(XVI.)

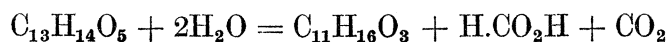


(XVII.)



(XVIII.)

The substances $C_{11}H_{16}O_3$ (products A and B, XV) are obtained from citrinin, which is a hydroxycarboxylic acid, in accordance with the equation :—



and it appears that this decomposition can only be explained by attributing the formula XVII to citrinin.

The only alternative is the related *o*-quinonoid formula (XVIII), and this is improbable in view of the superior stability of *p*-benzoquinones ; moreover, the yellow colour is in good agreement with the *p*-quinone structure.

The constitution XVII serves to illustrate the whole chemical behaviour of the colouring matter, and we are now engaged in synthetical experiments, with the object of confirming the correctness of these deductions. It may be noted that the carbon skeleton of XVII contains two straight chains of six carbon atoms each, joined at their γ -positions by a thirteenth carbon atom.