

[CONTRIBUTION FROM THE INSECTICIDE DIVISION, BUREAU OF CHEMISTRY AND SOILS]  
**ROTENONE. XIX. THE NATURE OF THE ALKALI SOLUBLE  
 HYDROGENATION PRODUCTS OF ROTENONE AND ITS  
 DERIVATIVES AND THEIR BEARING ON THE STRUCTURE OF  
 ROTENONE**

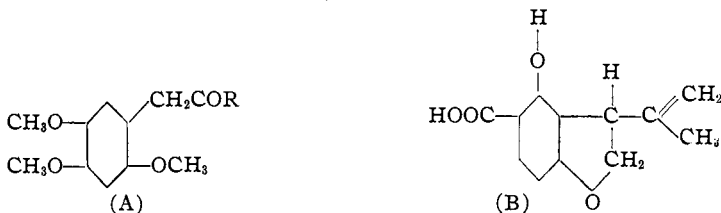
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In the early investigations on the structure of rotenone Takei<sup>1</sup> suggested the presence of a lactone group, and Butenandt<sup>2</sup> believed that he had evidence of its presence in rotenol and also in rotenone because the latter gave an alkali-soluble compound on hydrogenation in ammoniacal solution. In the course of our earlier work, we obtained from a number of rotenone derivatives by hydrogenation in neutral solutions, alkali-soluble products which we believed to be acids.<sup>3</sup> We also observed that these products were of very weak acidic properties, were displaced from their salts by carbon dioxide, and could not be successfully titrated. It might have been suspected that they were phenols rather than acids, except for the complete absence of the ferric chloride color test.

After the structure of the methoxyl-containing part of derritol methyl ether had been established as (A)



and it was shown that this derivative behaved like rotenone and many of its related compounds with respect to hydrogenation and yielded a corresponding acid, it became evident that the grouping involved was located in the part of the molecule (R) which yielded tubaic acid.

From theoretical considerations it was impossible to reconcile the formula for tubaic acid postulated by Takei (B) or any similar scheme, with the presence of a lactone group in that part of the molecule, and we were therefore inclined to believe that tubaic and isotubaic acids were secondary reaction products in spite of the fact that they were always obtained on oxidation or alkali fusion of numerous rotenone derivatives. A general exception to this rule was the fact that none of the so-called acids obtained by hydrogenation gave tubaic, isotubaic or dihydrotubaic acid by either process.

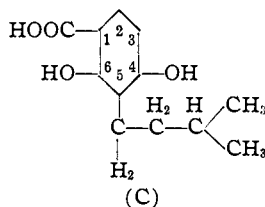
<sup>1</sup> S. Takei, *Biochem. Z.*, **157**, 1 (1925).

<sup>2</sup> A. Butenandt, *Ann.*, **464**, 253 (1929).

<sup>3</sup> To avoid confusion the names of the alkali-soluble hydrogenation products originally termed acids are retained.

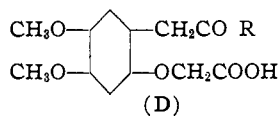
We have now made a further study of the hydrogenation products of tubaic acid on the one hand and of derrisic acid on the other, and the results apparently explain the nature of the alkali-soluble hydrogenation products of rotenone and its derivatives.

In our last communication<sup>4</sup> it was reported that tubaic acid is hydrogenated to a tetrahydro compound of formula  $C_{12}H_{16}O_4$  which we proved to be a substituted dihydroxybenzoic acid, in all probability to be expressed by formula (C). Both hydroxyls in this compound are easily acetylated, but only one is easily methylated. From further considerations it is fairly certain that the hydroxyl in position 6 is the one which resists methylation, although it gives a strong color test with ferric chloride.



These results are strictly analogous to those which were obtained in a parallel study of derrisic acid.

Derrisic acid was correctly expressed in a previous communication<sup>5</sup> by the partial formula (D) in which R represented the tubaic acid part of the molecule, containing, as was supposed, the lactone group.



Derrisic acid was found to yield on hydrogenation under pressure a mixture of dihydro ( $C_{23}H_{26}O_8$ ), and tetrahydro ( $C_{23}H_{28}O_8$ ) derrisic acids. Like tetrahydro-tubaic acid, the latter could be isolated owing to its insolubility in chloroform.

It was also found that the ethyl ester of derrisic acid readily yielded the same tetrahydro acid even at atmospheric pressure and that the ester of the tetrahydro acid could be separated from the dihydro ester by extracting the cold acetic ester solution of the mixture with aqueous alkali.

Thus it was found that derrisic acid undergoes the same reaction on hydrogenation as does rotenone.

Tetrahydroderrisic acid is optically inactive, gives a strong ferric chloride color test and is easily methylated by dimethyl sulfate with the formation of a methyltetrahydroderrisic acid methyl ester which separates in crystalline form from the alkaline solution during the process. Both the methyl ester and the corresponding acid give a color test with ferric chloride.

The presence of a free hydroxyl group in the methyl ester is also demonstrated by the formation of a mono acetyl derivative which gives no phenol test with ferric chloride.

Tetrahydroderrisic acid itself when boiled with acetic anhydride yields a

<sup>4</sup> Haller and LaForge, *THIS JOURNAL*, **53**, 4460 (1931).

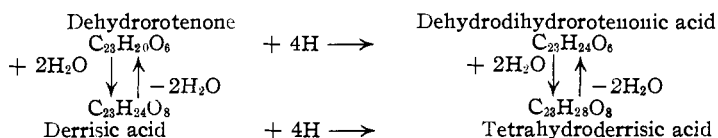
<sup>5</sup> LaForge, Haller and Smith, *ibid.*, **53**, 4400 (1931).

light yellow monoacetyl compound of formula  $C_{25}H_{26}O_7$ , which gives no phenol reaction. This compound is identical with the product obtained from dehydrodihydrotrotenonic acid  $C_{23}H_{24}O_6$ , the alkali-soluble hydrogenation product of dehydrotrotenone, by the same treatment. When the acetyl group is removed by saponification the original dehydrodihydrotrotenonic acid is obtained.

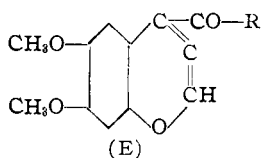
In a previous communication<sup>6</sup> we reported that this dehydrodihydrotrotenonic acid yielded an acid of formula  $C_{23}H_{26}O_7$  on treatment with zinc dust in alcoholic aqueous alkaline solution. A re-examination of this product showed that as ordinarily prepared it was always contaminated with a small quantity of starting material, which led to the erroneous analysis. The compound could, however, be easily purified by treatment with chloroform, which dissolves the dehydrodihydrotrotenonic acid, leaving the pure compound which then analyzed for, and was identical with, tetrahydroderrisic acid,  $C_{23}H_{28}O_8$ . Tetrahydroderrisic acid is most easily prepared by the last-mentioned method.

Tetrahydroderrisic acid, therefore, by the action of acetic anhydride reverts through the acetyl derivative with loss of two moles of water to dehydrodihydrotrotenonic acid. This is the reverse process of its formation by alkaline hydrolysis from dehydrodihydrotrotenonic acid with addition of two moles of water.

An analogous behavior has been observed in the case of deguelic acid<sup>7</sup> which reverts to dehydrodeguelin by treatment with acetic anhydride. The same process occurs in the case of derrisic and isoderrisic acids, which are converted into dehydro and isodehydrotrotenone by the same agent. These relations are expressed by the formulas in the following chart



Dehydrodihydrotrotenonic acid is easily methylated, and the methylated compound is converted by alkaline hydrolysis into 4-methyltetrahydroderrisic acid, identical with the product obtained by methylation of tetrahydroderrisic acid.



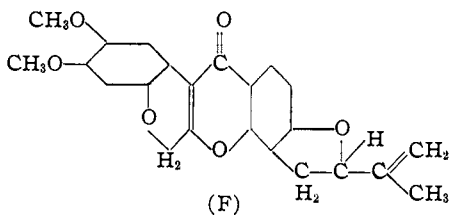
In one of our recent publications<sup>5</sup> we expressed the formula of dehydrotrotenone by (E). This formula was open to serious objections, but it served to explain the characteristic reaction of the compound under the assumption that a lactone group was contained in the tubaica acid part of the molecule. It has now become evident that the

<sup>6</sup> LaForge and Smith, *THIS JOURNAL*, 52, 3603 (1930).

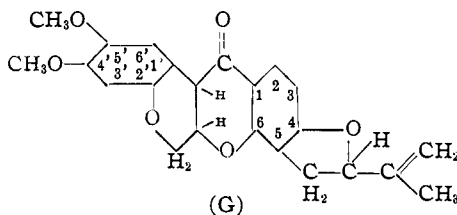
<sup>7</sup> Clark, *ibid.*, 52, 313 (1931).

lactone group is not present in rotenone or any of its derivatives, and we now suggest an important modification of this formula based on the results described in this article.

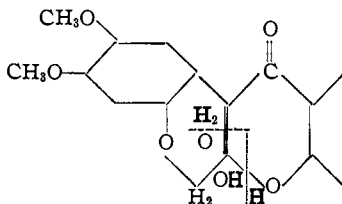
Dehydrorotenone should now be expressed by the complete formula (F)



and it would be derived from rotenone (G) by loss of two hydrogen atoms.

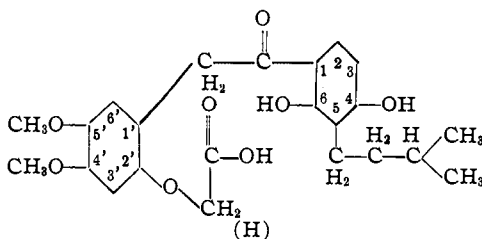


Derrisic acid is obtained from dehydrorotenone by the action of alcoholic alkali, the process being one of hydrolysis as follows

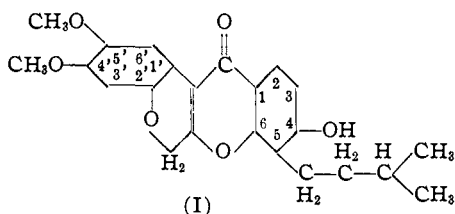


When derrisic acid is converted into dehydrorotenone by acetic anhydride, the reverse process, dehydration occurs.

Tetrahydroderrisic acid is now represented by the complete formula (H)

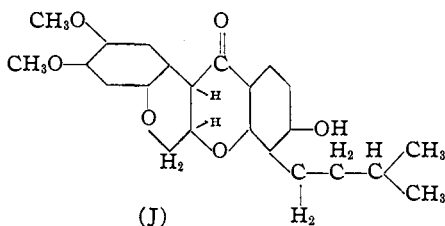


and dehydrodihydroderrisic acid derived from it by dehydration by (I).



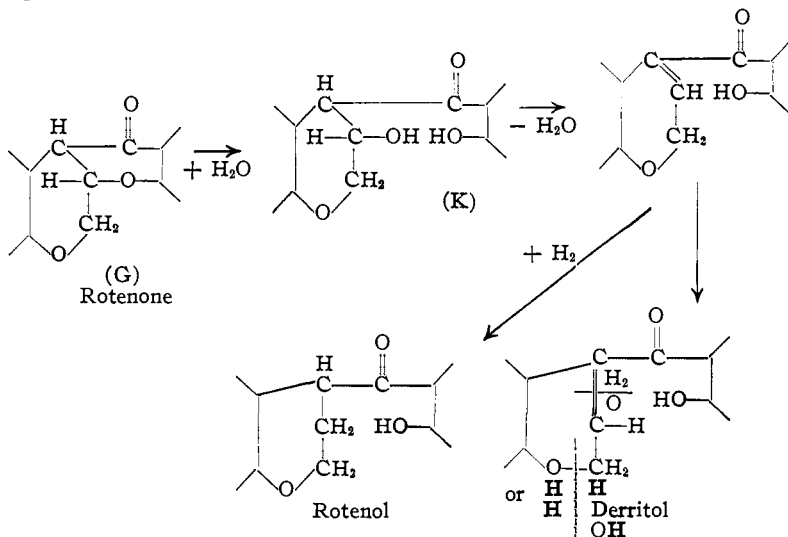
Dehydrodihydrorotenonic acid is acetylated in position 4 to form its acetyl derivative.

Dihydrorotenonic acid, which is obtained from rotenone (G) by hydrogenation, with opening of the oxide ring and loss of an asymmetric center would consequently be represented by formula (J). In tetrahydroderrisic



acid (H) the hydroxyl group in position 4 is easily methylated, but the one in 6 is not. The methyl ester of methylated tetrahydroderrisic acid is not soluble in alkali, but it is easily acetylated in position 6 under conditions which lead to the formation of dehydro compounds in cases where the carboxyl group is free.

Tetrahydroderrisic acid therefore contains two phenolic hydroxyl groups. The one in position 6 gives the ferric chloride color test as in the



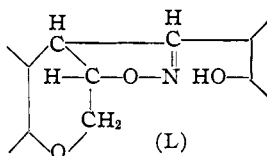
case of derrisic acid and certain other compounds, including rotenol, which contain the phenol group in this position.

The mechanism of the reactions leading to the formation of derritol and rotenol is with slight modification essentially the same as indicated in our previous article and are expressed by the preceding formulas.

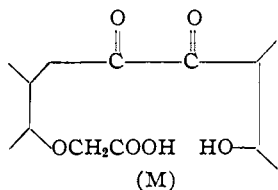
Derritol is then a diphenol, and rotenol is a monophenol. This is in agreement with the observation that both derritol monomethyl ether and rotenol give phenol color reactions although both are insoluble in alkali. In fact, aside from the true acids containing the carboxyl group, all compounds so far observed are insoluble in alkali except those containing a free phenolic group in position 4 on the tubaic acid side (rotenonic acid) or one in position 2' on the derric acid side (derritol). It is probable that the insolubility of those compounds containing only one free phenol group in position 6 is dependent on the presence of a carbonyl group in position 1 since rotenone isoxime and the related compounds are alkali soluble.<sup>2</sup>

Rotenone isoxime would in all probability contain the grouping (L) and would be formed from the grouping (K) with loss of one molecule of water.

A renewed attempt to acetylate rotenol led to a product which gave no phenol reaction with ferric chloride, although it failed to crystallize.



As a further confirmation of the formula for derrisic acid we have prepared the corresponding 1,2-diketone from isoderrisic acid. Isoderrisic acid, as would be expected, reacted with nitrous acid to give a compound containing the grouping (M) indicated below.



It follows from the results described above that the rotenone molecule does in fact contain the nucleus of tubaic acid modified as to the point of attachment of the alkyl side chain as indicated in Formula D.

### Experimental

**Tetrahydroderrisic Acid.**—One gram of derrisic acid was reduced with 0.5 g. of active platinum catalyst in 40 cc. of acetic ester under 50 pounds pressure for about two hours. The solution was filtered, the solvent removed and the residue recrystallized from 50% alcohol.

The first product was a mixture of dihydro- and tetrahydroderrisic acids. The compound was obtained pure by repeated extraction of the mixture with chloroform, which left most of the tetrahydro derivative undissolved. It was finally recrystallized from 50% alcohol. It melted at 204–206° and gave a positive ferric chloride test. The yield was about 0.3 g.

*Anal.* Subs., 0.0688, 0.0758: CO<sub>2</sub>, 0.1616, 0.1765; H<sub>2</sub>O, 0.0405, 0.0443. Calcd. for C<sub>23</sub>H<sub>28</sub>O<sub>8</sub>: C, 63.88; H, 6.48. Found: C, 64.08, 63.50; H, 6.54, 6.50.

The same compound was obtained by hydrogenation of derrisic acid ethyl ester at ordinary pressures. About the calculated volume of hydrogen was absorbed in a

few minutes, after which the acetic ester solution was cooled with ice and rapidly extracted with 2% potassium hydroxide solution.

The aqueous alkaline solution was allowed to stand for a few minutes at ordinary temperature to saponify the ester, and then acidified. The precipitated mixture, which contained very little of the dihydro compound, was filtered off, and recrystallized from 50% alcohol, and the dried material was extracted with chloroform and recrystallized from 50% alcohol. It melted at 204–206°.

**Tetrahydroerrisic Acid from Dehydrodihydrorotenonic Acid.**—Dehydrodihydrorotenonic acid was boiled with zinc dust in aqueous alcoholic potassium hydroxide solution as described in a previous article.<sup>8</sup> The resulting product (formerly called  $\beta$ -hydroxyrotenonic acid) was extracted with chloroform, which removed a small quantity of unchanged dehydrodihydrorotenonic acid. It was then recrystallized from 50% alcohol. It melted at 206°. It was shown by the mixed melting point and optical examination of the crystals to be identical with tetrahydroerrisic acid. The substance is obtained more easily and in better yield by this method. It was optically inactive.

*Anal.* Subs., 0.0745: CO<sub>2</sub>, 0.1757; H<sub>2</sub>O, 0.0433. Calcd. for C<sub>28</sub>H<sub>32</sub>O<sub>8</sub>: C, 63.88; H, 6.48. Found: C, 64.31; H, 6.46.

**Ethyl Ester of Tetrahydroerrisic Acid.**—This derivative was obtained from tetrahydroerrisic acid prepared by both the above-mentioned methods. One part of the acid was boiled with twenty parts of absolute ethyl alcohol containing 1% of sulfuric acid, for half an hour. The ester separated on cooling and was recrystallized from 95% alcohol. It melted at 180°, gave a strong color test with ferric chloride and was easily soluble in dilute cold alkali.

*Anal.* Subs., 0.0802: CO<sub>2</sub>, 0.1918; H<sub>2</sub>O, 0.0460. Calcd. for C<sub>28</sub>H<sub>32</sub>O<sub>8</sub>: C, 65.22; H, 6.96. Found: C, 65.22; H, 7.11.

**4-Methyltetrahydroerrisic Acid and 4-Methyltetrahydroerrisic Acid Methyl Ester.**—Four grams of tetrahydroerrisic acid was dissolved in 35 cc. of 5% potassium hydroxide solution. The solution was agitated with a mechanical stirrer while 7 g. of dimethyl sulfate was slowly added over a period of one-half hour. The agitation was continued for two hours, the solution being kept alkaline with further addition of alkali. The methyl ester of methyl tetrahydroerrisic acid separated in crystalline form from the alkaline solution. It was filtered off and recrystallized from methyl alcohol. In some experiments the crystals contained a gummy impurity which was easily washed off with methyl alcohol. It crystallized in stout heavy prisms. The yield was 2.5 g. The ester melted at 111–112°. The ferric chloride test was positive.

*Anal.* Subs., 0.0802 g., 3.345 mg.: CO<sub>2</sub>, 0.1910, 8.010; H<sub>2</sub>O, 0.0478, 2.076. Subs., 0.0207: cc. of thiosulfate (1 cc. = 0.000517 CH<sub>3</sub>O),<sup>9</sup> 10.85. Calcd. for C<sub>28</sub>H<sub>32</sub>O<sub>8</sub>: C, 65.21; H, 6.94; 4CH<sub>3</sub>O, 26.95. Found: C, 64.95, 65.30; H, 6.64, 6.89; CH<sub>3</sub>O, 27.09.

The corresponding 4-methyltetrahydroerrisic acid was obtained by saponification of the ester. The alkaline solution obtained on methylation also contained the free acid, which was isolated by acidification and extraction with ether. The acid after recrystallizing from benzene melted at 158°. When it was again recrystallized from acetic acid, the melting point was 164°. It gave a positive test with ferric chloride.

*Anal.* Subs., 0.0797: CO<sub>2</sub>, 0.1887; H<sub>2</sub>O, 0.0472. Subs., 0.0211: thiosulfate solution (1 cc. = 0.000581 CH<sub>3</sub>O), 7.56 cc.; 0.0215; thiosulfate solution (1 cc. = 0.000517 CH<sub>3</sub>O), 8.65 cc. *Titration.* Subs., 0.0210: N/20 KOH, 1.00 cc. Calcd. for C<sub>24</sub>H<sub>30</sub>O<sub>8</sub>: C, 64.57; H, 6.72; 3CH<sub>3</sub>O, 20.85; mol. wt. 446. Found: C, 64.57; H, 6.54; CH<sub>3</sub>O, 20.77, 20.80; mol. wt. 420.

<sup>8</sup> La Forge and Smith, *THIS JOURNAL*, **52**, 3606 (1930).

<sup>9</sup> F. Vieböck and Schwappach, *Ber.*, **63**, 2818 (1930).

**6-Acetyl-4-methyltetrahydroderrisic Acid Methyl Ester.**—Seven-tenths of a gram of the ester was acetylated by boiling with 10 cc. of acetic anhydride containing 5% of acetic acid and 0.2 g. of sodium acetate. The boiling was continued for thirty minutes, after which methyl alcohol was added and the solution concentrated to about 5 cc. The product crystallized on addition of water and was recrystallized from methyl alcohol, from which it separates in long white needles. It melted at 111° and gave no phenol test with ferric chloride.

*Anal.* Subs., 0.0741: CO<sub>2</sub>, 0.1763; H<sub>2</sub>O, 0.0449. Subs., 0.0207: thiosulfate (1 cc. = 0.000517 CH<sub>3</sub>O), 9.90 cc. Calcd. for C<sub>27</sub>H<sub>34</sub>O<sub>8</sub>: C, 64.54; H, 6.77; 4CH<sub>3</sub>O, 24.70. Found: C, 64.88; H, 6.73; CH<sub>3</sub>O, 24.72.

**Derric Acid from Methyltetrahydroderrisic Acid.**—Two grams of substance oxidized with 6 cc. of 30% hydrogen peroxide in 5% potassium hydroxide solution yielded 0.4 g. of derric acid. The melting point was 170°.

*Anal.* Subs., 0.0215: AgI, 0.0370. Calcd. for C<sub>12</sub>H<sub>14</sub>O<sub>7</sub>: 2CH<sub>3</sub>O, 22.96. Found: CH<sub>3</sub>O, 22.75.

**4-Acetyldehydrodihydrorotenonic Acid from Tetrahydroderrisic Acid.**—One-half gram of substance was boiled for ten minutes with 7 cc. of acetic anhydride containing 5% of acetic acid and 0.15 g. of anhydrous sodium acetate. An equal volume of alcohol was added, and the solution was boiled for a few minutes longer. On cooling the acetyl compound separated out in light yellow prismatic needles. It was recrystallized from alcohol, in which it is soluble with difficulty. It melted at 202° and gave no ferric chloride test. The yield was about 0.2 g.

*Anal.* Subs., 0.0823, 0.0783: CO<sub>2</sub>, 0.2062, 0.1953; H<sub>2</sub>O, 0.0429, 0.0422. Calcd. for C<sub>25</sub>H<sub>26</sub>O<sub>7</sub>: C, 68.48; H, 5.91. Found: C, 68.33, 68.02; H, 5.73; 5.99.

**4-Acetyldehydrodihydrorotenonic Acid from Dehydrodihydrorotenonic Acid.**—One gram of dehydrodihydrorotenonic acid was boiled with 15 cc. of acetic anhydride, 1 cc. of acetic acid and 0.25 g. of anhydrous sodium acetate for fifteen minutes. An equal volume of alcohol was added, and the solution boiled for a few minutes. The substance was recrystallized from alcohol and melted at 202°. It was identical with the one obtained from tetrahydroderrisic acid described above, as determined by the mixed melting point and crystal form. The yield was 0.8 g.

*Anal.* Subs., 0.0710: CO<sub>2</sub>, 0.1782; H<sub>2</sub>O, 0.0371. Subs., 0.0227: AgI, 0.0245. Calcd. for C<sub>25</sub>H<sub>26</sub>O<sub>7</sub>: C, 68.48; H, 5.91; 2CH<sub>3</sub>O, 14.13. Found: C, 68.45; H, 5.80; CH<sub>3</sub>O, 14.26.

On saponification with alcoholic potassium hydroxide it yielded the original dehydrodihydrorotenonic acid.

**4-Methyldehydrodihydrorotenonic Acid.**—Two grams of dehydrodihydrorotenonic acid was dissolved with gentle warming in about 25 cc. of 5% potassium hydroxide. The solution was agitated with a mechanical stirrer and 6 cc. of dimethyl sulfate was added over a period of about one hour. The reaction was continued for another hour with further addition of alkali from time to time. The product separated crystalline during the process and was filtered off, washed with dilute alkali and recrystallized from alcohol. It formed long nearly white prisms melting at 169°.

*Anal.* Subs., 0.0814: CO<sub>2</sub>, 0.2090; H<sub>2</sub>O, 0.0460. Calcd. for C<sub>24</sub>H<sub>26</sub>O<sub>6</sub>: C, 70.24; H, 6.34. Found: C, 70.02; H, 6.28.

**4-Methyltetrahydroderrisic Acid from 4-Methyldehydrodihydrorotenonic Acid.**—One gram of 4-methyldehydrodihydrorotenonic acid was refluxed in 90 cc. of alcohol with 10 cc. of 15% potassium hydroxide solution and 2 g. of zinc dust for four hours. The solution was then filtered into dilute hydrochloric acid solution. The precipitate was filtered off and dissolved in ether. The ether solution was extracted with dilute



alkali, and the alkaline extract was acidified with dilute hydrochloric acid. The precipitate was filtered off, washed with water and dried. It was recrystallized from glacial acetic acid. It melted at 163–164°. When it was mixed with an equal quantity of 4-methyltetrahydroderrisic acid the melting point was 162–163°.

*Anal.* Subs., 0.00248: thiosulfate (1 cc. = 0.000517 OCH<sub>3</sub>), 10.10 cc. Calcd. for C<sub>24</sub>H<sub>30</sub>O<sub>8</sub>: 3CH<sub>3</sub>O, 20.85. Found: 21.05.

**1,2-Diketone from Isoderrisic Acid.**—One and a half grams of isoderrisic acid was suspended in 12 cc. of glacial acetic acid, and cooled with an ice-bath, and 8 g. of amyl nitrite was added. Twelve cc. of a mixture of equal parts of concentrated hydrochloric acid and glacial acetic acid was added over a period of thirty minutes, and the solution was allowed to stand for several hours at room temperature. The isoderrisic acid gradually went into solution with slow gas evolution. Water was added, and the products were extracted with ether. The ether solution was washed with water to remove the acetic acid, and then with dilute sodium carbonate. The alkaline solution was acidified and extracted with ether. The ether residue crystallized on standing. It was washed with benzene and recrystallized from a small volume of glacial acetic acid, from which it separated in bright yellow heavy prisms. It contained solvent of crystallization which was expelled in vacuum at 100°. The yield was 0.5 g. It gave a positive ferric chloride test and melted at 195°.

*Anal.* Subs., 0.0712: CO<sub>2</sub>, 0.1631; H<sub>2</sub>O, 0.0336. Subs., 0.02125: thiosulfate (1 cc. = 0.000517 CH<sub>3</sub>O), 5.65 cc. Calcd. for C<sub>23</sub>H<sub>22</sub>O<sub>9</sub>: C, 62.64; H, 4.98; 2CH<sub>3</sub>O, 14.02. Found: C, 62.46; H, 5.24; CH<sub>3</sub>O, 13.74.

### Summary

Derrisic acid is hydrogenated to tetrahydroderrisic acid.

Tetrahydroderrisic acid is also obtained by alkaline hydrolysis of dehydrodihydrorotenonic acid. Conversely, by the process of dehydration, derrisic and tetrahydroderrisic acids are converted into dehydrorotenone and dehydrodihydrorotenonic acid.

Both dehydrodihydrorotenonic acid and tetrahydroderrisic acid are phenols which can be methylated in position 4. Tetrahydroderrisic acid is a diphenol, and its ester can be acetylated in position 6. Derritol is a diphenol and rotenol a monophenol. All rotenone derivatives which have only one free phenol group in position 6 are alkali insoluble although they give a positive color test with ferric chloride. The lactone group is not present in rotenone or any of its derivatives, and the alkali-soluble hydrogenation products which were supposed to contain the carboxyl group are not acids but phenols. All the reactions of rotenone and its derivatives are now easily explained by the formula:

