2. The various groups have been arranged in order of their migratory tendencies. Definite values have been assigned when possible.

3. *m*-Methoxy cyanobenzene, *m*-methoxybenzamide, benzoyl-4,4′-di-isopropyltriphenylmethane, and 4,4′-di-isopropyltriphenylmethane have been described, in addition to the ten pinacols, none of which has previously been reported in the literature.

URBANA, ILLINOIS

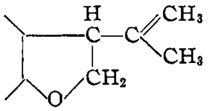
[CONTRIBUTION FROM THE INSECTICIDE DIVISION, BUREAU OF CHEMISTRY AND SOILS]

ROTENONE. VIII. ISOMERIC HYDROXY ACIDS AND THEIR RELATION TO DEHYDROROTENONE

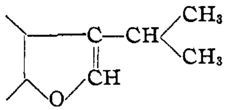
BY F. B. LAFORGE AND L. E. SMITH

RECEIVED MAY 14, 1930 PUBLISHED SEPTEMBER 5, 1930

Rotenone is converted by a number of oxidizing agents into dehydrorotenone, with the loss of two hydrogen atoms. In a recent article, Butenandt has shown that a double bond is formed in this process.[1] Although this new double bond cannot be reduced by catalytic hydrogenation, its presence in dehydrorotenone can be demonstrated by the reaction of Diels,[2] which involves a condensation of a conjugated system with maleic anhydride. It has also been demonstrated that the optically active tubaic acid obtained by cleavage of rotenone with alcoholic potassium hydroxide is converted into inactive rotenic acid under the same conditions by which rotenone is converted into isorotenone and that isorotenone yields rotenic acid by cleavage with alcoholic potassium hydroxide.[1,3] It follows from these facts with a fair degree of certainty that the isomerism between rotenone and isorotenone is due to the same cause as the isomerism between tubaic and rotenic acids. The change involved may be illustrated by the tentative formulas I and II. In these formulas the positions of attachment of the side chain, as well as that of the hydroxyl and carboxyl groups not shown in the figures are as yet undetermined.[4]



I. Tubaic acid



II. Rotenic acid

Since an asymmetric center disappears in this process and since isorotenone is optically active, Butenandt infers that this compound still contains one or more asymmetric carbon atoms in the other half of the molecule, about which little was known to him at the time.

---

[1] Butenandt and Hildebrandt, *Ann.*, **477**, 245 (1929).

[2] Diels and Adler, *ibid.*, **460**, 102 (1928).

[3] Takei, *Ber.*, **63**, 508 (1930); Haller and LaForge, THIS JOURNAL, **52**, 2480 (1930).

[4] Haller and LaForge, *ibid.*, **52**, 3207 (1930).

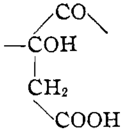
Dehydroisorotenone described by Butenandt and by us[5] is optically inactive whether prepared from isorotenone by the action of iodine and potassium acetate or by the conversion of dehydrorotenone into its isomer by sulfuric acid. It follows from this, as Butenandt has pointed out, that an asymmetric center has disappeared in the formation of the dehydro derivatives.

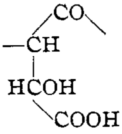
This theory seemed to be in agreement with the principal facts observed by us regarding the mechanism of the formation of the dehydro compounds.[5]

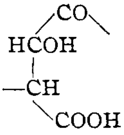
We have described an intermediary product, rotenolone, isolated from the reaction mixture obtained when iodine and potassium acetate react on rotenone.[5] Rotenolone is an hydroxy rotenone and is easily converted into dehydrorotenone by elimination of water.

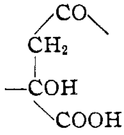
Dehydrorotenone is converted into a dihydroxy monobasic acid by the action of alcoholic potassium hydroxide, a reaction which is assumed to involve the addition of one molecule of water to the new double bond characteristic of the dehydro derivatives and another molecule of water to the lactone group to form the acid radical.

The resulting acid most likely contains one of the following groupings


III


IV


V


VI

Dehydrorotenone is converted by catalytic hydrogenation into dehydrodihydrorotenonic acid, which in turn is converted into an hydroxy acid which also contains the same grouping as the acid just referred to.[6] Both give derric acid on oxidation.

In a previous article we have shown that this oxidation product, which represents the part of the rotenone molecule containing the methoxyl groups, in all probability is of the nature of a dimethoxy phenyl malic acid and would therefore contain one of the groupings given above.[7] But since the carbonyl group in these groupings becomes a carboxyl group in derric acid, the possibilities are then limited to two combinations, since III and VI and IV and V become identical.

We have just pointed out the fact that the dehydro derivatives are formed from hydroxy derivatives of the rotenolone type by elimination

---

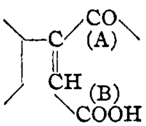
[5] LaForge and Smith, This Journal, **52**, 1094 (1930).

[6] We have designated acids of this type as dehydro hydroxy acids in previous articles because they were obtained from dehydro compounds, but since it is now fairly certain that they correspond to rotenonic acid, the prefix "dehydro" has been discontinued.

[7] LaForge and Smith, This Journal, **52**, 2878 (1930).

of water. This reaction is easily brought about by boiling the hydroxyl derivative or the corresponding acetyl compounds with alcoholic sulfuric acid. This reaction does not take place in the case of derric acid or either of the hydroxy acids from which it is obtained. For this reason the position of the hydroxyl group in rotenolone cannot be the same as in these acids.

If we assume that the hydroxy acids are formed by the addition of water to dehydrodihydrorotenonic acid of possible formula indicated, it will be apparent that there are a number of possibilities, depending on whether the hydroxyl is added at position A or B. If it is added at A, one asymmetric carbon atom arises, if at B, two are formed, and the number of possible compounds is multiplied by two, because the part of the molecule not involved in these changes already contains an asymmetric carbon atom. Because of the fact that derric acid and the two hydroxy acids which had been prepared did not revert to dehydro compounds when treated with alcoholic sulfuric acid, we were inclined to another theory regarding the nature of the dehydro compounds.[7]



We have, however, lately prepared two dihydrohydroxyrotenonic acids, isomeric with the one obtained by the action of alcoholic potassium hydroxide on dehydrodihydrorotenonic acid. These new acids are readily dehydrated by alcoholic sulfuric acid and give dehydrodihydrorotenonic acid. Because of these new facts it is now possible to bring our views into harmony with the theory of Butenandt. It is not possible to assign the position of the hydroxyl in any of the acids concerned but for convenience we will designate those compounds which are easily dehydrated as belonging to the alpha, and those which cannot be dehydrated to the beta series.

One of the two new alpha acids was prepared in two ways: by reducing rotenolone with hydrogen and platinum catalyst which yielded dihydrorotenolonic acid together with dihydrorotenolone, or by catalytic reduction of acetylrotenolone to dihydro-acetylrotenolone and dihydro-acetylrotenolonic acid. The latter is easily saponified to the hydroxy acid.

The second acid was obtained by oxidation of rotenonic acid with hydrogen peroxide in alkaline solution. The products obtained were an hydroxyrotenonic acid of formula $C_{23}H_{24}O_7$ together with some of the corresponding dehydro acid of formula $C_{23}H_{22}O_6$. The hydroxy acid is easily reduced by catalytic hydrogenation to the dihydro acid. Both of these isomeric dihydrohydroxy acids readily give dehydrodihydrorotenonic acid when treated with alcoholic sulfuric acid. From the acid ($C_{23}H_{24}O_7$) obtained directly from rotenonic acid, dehydrorotenonic acid was obtained for the first time, for it had not been possible to reduce the lactone ring in dehydrorotenone without reduction of the double bond so that dehydrodihydrorotenonic acid was always obtained. Dehydrorotenonic acid is readily hydrogenated to the dihydro derivative.

We have also made some alkaline peroxide oxidations on two other rotenone derivatives with rather unexpected results. The acid of formula $C_{23}H_{22}O_8$ (dihydrodehydrohydroxyrotenononic acid), described by us in a previous communication, obtained by the action of strong alcoholic potassium hydroxide on dihydrorotenonone yielded no derric acid or corresponding methoxyl-containing compound but dihydrotubaic acid as the only crystalline reaction product.

This fact is an additional proof that the reaction leading to the compounds of the rotenonone type do not take place in the part of the rotenone represented by tubaic acid, but in the other half of the molecule.

We have expressed the view in a previous article[5] that dihydrodehydrohydroxyrotenononic acid was formed by the opening of a lactone ring and not as Butenandt believed by a benzilic acid rearrangement. We have been able to prove our theory to be correct by the fact that the acid easily reverts to dihydrodehydrorotenonone by boiling in acetic acid solution.

Dehydrodihydrorotenonic acid did not yield derric acid on oxidation with hydrogen peroxide but gave the acid of formula[7] $C_{11}H_{12}O_7$ which we obtained from derric acid by permanganate oxidation.

We have made numerous attempts to separate derric acid into its optically active components. Its brucine salt crystallizes well, but after four recrystallizations the derric acid from it was still inactive. No other suitable alkaloid salts were obtained.

β-Dihydrohydroxyrotenonic Acid.—One and eight-tenths grams of dehydrodihydrorotenonic acid[5] was refluxed for four and one-half hours with 18 cc. of 15% potassium hydroxide, 54 cc. of ethyl alcohol and 3.6 g. of zinc powder. After removal of the zinc by filtration, the solution was acidified with dilute hydrochloric acid, and water was added until it became turbid. The white crystalline compound so obtained was recrystallized from dilute ethyl alcohol. The yield was 1.5 g. The compound begins to darken at 192° and melts at 198°.

Anal. Subs., 0.0727: CO_2, 0.1779; H_2O, 0.0425. Calcd. for $C_{23}H_{26}O_7$: C, 66.67; H, 6.27. Found: C, 66.73; H, 6.49.

Oxidation of β-Dihydrohydroxyrotenonic Acid to Derric Acid.—One and a half grams of the acid was dissolved in 18 cc. of 5% potassium hydroxide and to the hot solution 5 cc. of 30% hydrogen peroxide was added in small portions. A small amount of tarry matter which formed was removed mechanically. After being boiled to remove the excess of hydrogen peroxide the solution was cooled and acidified with dilute hydrochloric acid and extracted with ether. The ether solution dried over sodium sulfate gave on evaporation derric acid in a yield of 0.25 g. It was recrystallized from ethyl acetate–*n*-butyl ether, and melted at 170°. Mixed with derric acid it melted at 170°.

Acetyl α-Dihydrorotenolonic Acid (Acetyl α-Dihydrohydroxyrotenonic Acid).—Three grams of acetylrotenolone was reduced in ethyl acetate solution with 0.2 g. of platinum oxide catalyst. In about thirty minutes 252 cc. of hydrogen had been absorbed, and the reaction stopped. The theoretical quantity of hydrogen corresponding to two molecules is calculated as 295 cc. The solution was diluted with ether and extracted with ice-cold 2% aqueous potassium hydroxide solution. The material insoluble in alkali was isolated by evaporation of the dried ether–ethyl acetate solution. It was recrystallized from methyl alcohol and melted at 189°. It was identical with acetyldihydrorotenolone obtained from dihydrorotenone by the iodine potassium acetate method. The yield was 0.5 g. The aqueous alkaline extract yielded 2 g. of acetyldihydrorotenolonic acid melting between 210 and 214° with decomposition.

Anal. Subs., 0.0687: CO_2, 0.1668; H_2O, 0.0390. Calcd. for $C_{25}H_{28}O_8$: C, 65.79; H, 6.14. Found: C, 66.21; H, 6.31.

Dihydrorotenolonic Acid (**α-Dihydrohydroxyrotenonic Acid**).—This acid may be obtained either by saponification of acetyldihydrorotenolonic acid or by direct hydrogenation of rotenolone, and separation of the reaction mixture into neutral and acid fractions. By the last-mentioned method the yield of acid is small and hence the first procedure is to be preferred. Two grams of acetyldihydrorotenolonic acid was boiled for two hours with slightly more than the calculated quantity of half normal potassium hydroxide. The solution was acidified and the precipitated acid dissolved in ether. After drying and removal of the ether, a sirup was obtained which crystallized completely after seeding with crystals obtained by hydrogenation of rotenolone. The compound is extremely soluble in all reagents except water and petroleum ether. We have not succeeded in recrystallizing it.

Acetyldihydrorotenolonic acid readily gives dehydrodihydrorotenonic acid when boiled for about an hour with 10 parts of 10% alcoholic sulfuric acid and an equal volume of hot water is added to it. Dehydrodihydrorotenonic acid was identified by its melting point, mixed melting point and an optical examination of the crystals. The crude dihydrorotenolonic acid, treated in the same manner, gives the same compound.

Oxidation of Rotenonic Acid with Hydrogen Peroxide.—Two grams of rotenonic[8] acid is dissolved in 25 cc. of 5% potassium hydroxide and to the warm solution 30% hydrogen peroxide is added in small portions until a precipitate is produced. About 8 cc. is usually required. The reaction mixture is boiled for a few minutes and then cooled and saturated with carbon dioxide. A heavy precipitate is formed which is extracted with ether and the solution dried over sodium sulfate.[9] The ether residue contains two compounds. It is dissolved in methyl alcohol from which a small quantity of a yellow compound crystallized on cooling. It melted at 225°. The analysis agrees for dehydrorotenonic acid.

Anal. Subs., 0.0608: CO_2, 0.1551; H_2O, 0.0308. Calcd. for $C_{23}H_{22}O_6$: C, 70.05; H, 5.59. Found: C, 69.57; H, 5.61.

When the methyl alcoholic mother liquor is diluted with water the second crystalline compound is obtained which is recrystallized from dilute methyl alcohol. It melts at 137°, and the yield is 0.25 g. The analysis shows it to be an hydroxyrotenonic acid. The compound was dried to constant weight at 110° for analysis.

Anal. Subs., 0.0681, 0.0741: CO_2, 0.1671, 0.1817; H_2O, 0.0367, 0.0394. Subs., 0.0187: AgI, 0.0215. Calcd. for $C_{23}H_{24}O_7$: C, 66.99; H, 5.82; $2OCH_3$, 15.04. Found: C, 66.9, 66.87; H, 5.99, 5.90; OCH_3, 15.17. Subs., 0.0146: 0.375 cc. of *N*/10 KOH; mol. wt. calcd. 412; found, 390.

Isomeric α-Dihydrohydroxyrotenonic Acid.—One-half gram of α-hydroxyrotenonic acid was reduced in ethyl acetate solution with 0.1 g. of platinum catalyst. The theoretical volume of hydrogen for 1 molecule, 27 cc., was absorbed in a few minutes. The

---

[8] LaForge and Smith, This Journal, **51**, 2578 (1929).

[9] Most acids of the type of rotenolonic acid are insoluble in carbonates and are precipitated from alkaline solution by carbon dioxide.

solution was decanted from the platinum, evaporated to dryness and the substance recrystallized from dilute ethyl alcohol. The compound sinters somewhat, probably due to water or alcohol of crystallization, and melts at 132°. For analysis it was dried to constant weight at 110°.

Anal. Subs., 0.0608: CO_2, 0.1474; H_2O, 0.0342. Calcd. for $C_{23}H_{26}O_7$: C, 66.66; H, 6.28. Found: C, 66.11; H, 6.25.

Dehydrorotenonic Acid.—One gram of the hydroxyrotenonic acid was boiled for one and one-half hours with 10 cc. of 10% alcoholic sulfuric acid. When 3 cc. of water was slowly added to the boiling solution, a small quantity of a compound crystallized out at once. The solution was refluxed for fifteen minutes, cooled and the precipitate was filtered off and recrystallized from benzene. It melts at 275°. The yield was 0.13 g.

This compound is stable to alkali. Further study is being made on this substance. The alcoholic mother liquors were diluted with water, and a yellow crystalline compound was obtained which was recrystallized from methyl alcohol. It melted at 225–227°. When mixed with dehydrorotenonic acid obtained directly by the oxidation of rotenonic acid with hydrogen peroxide, the melting point showed no depression.

Dehydrodihydrorotenonic Acid from Dehydrorotenonic Acid.—Dehydrorotenonic acid was reduced in acetone solution with hydrogen with platinum catalyst in the usual manner. The theoretical amount of hydrogen for the 0.35 g. used, 20 cc., was absorbed in a few minutes. The solution was evaporated to dryness and the compound recrystallized from dilute ethyl alcohol. It melted at 221°. Mixed with dehydrodihydrorotenonic acid it melted at 221°. The two substances were compared optically by George L. Keenan of the Food, Drug and Insecticide Administration of the Department of Agriculture, and found to be identical.

"In ordinary light this material is of a sulfur-yellow color and consists of very fine needles. In parallel polarized light, crossed nicols, the extinction is straight and the sign of elongation negative. Nothing significant is shown in convergent polarized light with crossed nicols. The refractive indices are: $-n_\alpha = 1.470$ (commonly shown lengthwise); $n_\beta = 1.690$; $n_\gamma = 1.737$ (commonly shown crosswise); all ±0.003."

Oxidation of Dihydrodihydroxyrotenononic Acid[5] with Hydrogen Peroxide.—Two grams of the acid was dissolved in 30 cc. of 5% potassium hydroxide, and 8 cc. of 30% hydrogen peroxide was added in small portions. After boiling for a few minutes the solution was cooled and made acid with dilute hydrochloric acid. A light yellow material crystallized out, which was recrystallized from dilute methyl alcohol. It melted at 167°. The yield was 0.3 g. The compound contains no methoxyl group. When mixed with dihydrotubaic acid of melting point 167°, the melting point showed no depression.

Oxidation of Dehydrodihydrorotenonic Acid with Hydrogen Peroxide.—One and three-tenths grams of acid was dissolved in 17 cc. of 5% potassium hydroxide solution, and 5 cc. of 30% hydrogen peroxide was added in small portions. After boiling for a few minutes the solution was filtered from a small precipitate and cooled. On acidifying with dilute hydrochloric acid, a crystalline material was obtained which was recrystallized from 95% ethyl alcohol. It melted at 262° with decomposition. The yield was 0.2 g.

Anal. Subs., 0.0658: CO_2, 0.1247; H_2O, 0.0272. Calcd. for $C_{11}H_{12}O_7$: C, 51.56; H, 4.68. Found: C, 51.68; H, 4.59. Subs., 0.0187: 1.55 cc. of $N/10$ KOH; mol. wt. calcd., 256; found, 241.

The compound is identical with the acid obtained by the oxidation of derric acid.

Dihydrorotenonone from Dehydrodihydrorotenononic Acid.—When dehydrodihydrorotenononic acid is boiled with glacial acetic acid for a few minutes the solution becomes very dark and on cooling, a yellow compound crystallizes out, melting at 288°.

The yield is about 25% of the theoretical. Mr. Keenan has found the compound to be optically identical with dihydrorotenonone.

Anal. Subs., 0.0647: CO_2, 0.1605; H_2O, 0.0285. Calcd. for $C_{23}H_{20}O_7$: C, 67.61; H, 4.93. Found: C, 67.66; H, 4.89.

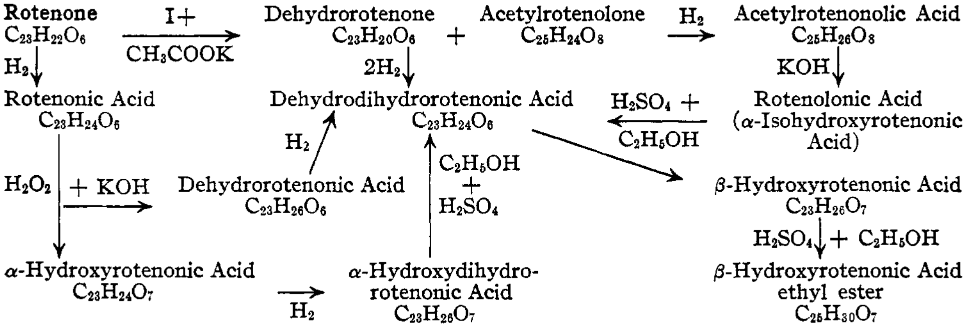
Summary

Dehydrodihydrorotenonic acid is formed by catalytic reduction of dehydrorotenone. It is also produced by dehydration of α-hydroxyrotenonic acids by alcoholic sulfuric acid. Two isomeric alpha acids were prepared.

Dehydrodihydrorotenone adds water when boiled with alcoholic potassium hydroxide to form β-hydroxyrotenonic acid which cannot be dehydrated but yields an ester when treated with alcoholic sulfuric acid. β-Hydroxyrotenonic acid yields derric acid on peroxide oxidation.

Dehydrodihydrorotenonic acid yielded no derric acid but its oxidation product of formula $C_{11}H_{12}O_7$. By the same treatment dihydrodehydrohydroxyrotenononic acid gave dihydrotubaic acid.

Attempts to separate derric acid into optical isomers were unsuccessful. The reactions involved are illustrated in the table.



WASHINGTON, D. C.