THE DETERMINATION OF THE STRUCTURE OF ROTENONE

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About three-quarters of a century ago travelers in the East Indies, South America, and tropical Africa reported the use of certain plants as an aid in catching fish. Botanists have since shown that some of the most potent of these fish-poisoning plants, commonly called tuba, timbo, cubé, and haiari, belong to the family *Fabaceae*, or *Papilionaceae*, and the genera *Derris, Milletia, Tephrosia,* and *Lonchocarpus.* These genera owe their toxic properties to one or more chemically closely related substances, of which the most important is rotenone.

The employment of derris extract as an insecticide by gardeners in the East Indies has long been a common practice. As early as 1848 Oxley (34) reported the use of tuba root (*D. elliptica*) for this purpose in connection with nutmeg cultivation. A number of related species have since been found to have insecticidal value.

Recent studies have shown that, although rotenone and other fish poisons have a strong toxic action when introduced into the blood stream of warm-blooded animals, they are relatively non-toxic when taken by mouth (1).

In the last few years there has been an increasing use of derris products as insecticides, and the plant is now cultivated in the Dutch East Indies and the Malay States. Derris root and its concentrated extracts, as well as rotenone itself, are now articles of commerce.

It appears that rotenone was first isolated in 1895 by Geoffroy (8) from a plant native to French Guiana and called *Robinia nicou.* The substance was reported to melt at 162°C. and was named by the author nicouline. Tests which the author de-

scribed in detail were made with nicouline on several insects and also on warm-blooded animals. The same plant, now called *Lonchocarpus nicou*, has since been shown to contain rotenone (6), which is therefore identical with Geoffroy's nicouline.

Kazuo Nagai in 1902 isolated from the roots of *Derris chinensis* a crystalline substance, melting at 163°C., which he called rotenone (33). He attempted to determine its molecular weight and prepared the phenylhydrazone.

In 1911 Lenz (32) extracted from *Derris elliptica* a compound reported to melt at 158°C. and named it derrin; five years later Ishikawa (18) isolated the identical substance from the same plant and observed that it was optically active. He gave it the name tubatoxin. In the later literature the name rotenone has been generally accepted.

Kariyone (19) observed the presence of methoxyl in rotenone and established the presence of one unsaturated linkage by its catalytic reduction to dihydrorotenone. He also prepared the oximes of rotenone and dihydrorotenone and made the important observation that rotenone was cleaved by alkali and yielded an acid of the formula $C_{12}H_{12}O_4$ (20), which he called tubaic acid. Tubaic acid was shown to contain one double linkage and gave the color reactions of a phenol. By alkali fusion it was converted into the isomeric isotubaic (rotenic) acid (42, 11). Dihydrorotenone yielded dihydrotubaic acid, identical with the reduction product of tubaic acid (20).

Takei (42) found that rotenone could be isomerized to isorotenone, and that by mild oxidation it yielded a yellow derivative, later shown to be dehydrorotenone. By energetic oxidation he prepared rotenononone and converted it into a hydroxy acid. The correct empirical formula for rotenone, $C_{23}H_{22}O_6$, was first proposed by Butenandt (2) in his inaugural dissertation, and this formula was confirmed by Takei (43).

In 1928 Butenandt (3) published an article on rotenone, in which he reported the following observations. Of the six oxygen atoms of rotenone, two are present in the form of methoxyl groups and another as a carbonyl group, while the other three cannot be directly detected. It was suspected that one of these

was in the form of an indifferent ether linkage, while certain reactions indicated that the remaining two were in the form of a lactone group.[1] By energetic reduction, both the unsaturated linkage and the ketone group can be reduced and the resulting dihydrodesoxyrotenone, $C_{23}H_{26}O_5$, can be calculated to be derived from the hydrocarbon $C_{21}H_{28}$. From the hydrogen content of a hydrocarbon of this formula, it can be assumed that two benzene rings are present in rotenone, and the remarkable stability of dihydrodesoxyrotenone indicates that all carbon atoms are directly connected with each other.

If rotenone is allowed to react with hydroxylamine or hydrazine in alkaline solution, the resulting derivatives are isomeric with those prepared in acid or neutral solutions, and exhibit the properties of phenols.

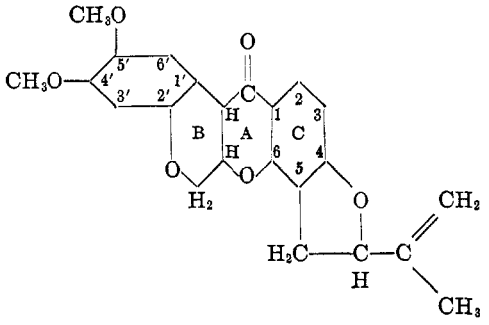
By treatment with zinc dust and alkali in alcoholic solution, rotenone yields two products, one of which, derritol, is alkali-soluble, is represented by the formula $C_{21}H_{22}O_6$, and gives the reactions of a phenol. The other compound, which has been called rotenol, is alkali-insoluble, and is represented by the formula $C_{23}H_{24}O_6$.

A number of oxidizing agents easily convert rotenone into dehydrorotenone, a yellow compound of formula $C_{23}H_{20}O_6$. Unlike rotenone, dehydrorotenone is not cleaved by alkali but is converted with addition of two moles of water into derrisic acid of the formula $C_{23}H_{24}O_8$.

The observations briefly described above have proved to be of special importance as a basis for subsequent work on the part of three groups of investigators, work which led to the determination of the complete structure of rotenone and of practically all

[1] The evidence for the presence of a lactone group was seen in the formation of derrisic acid by hydrolysis of dehydrorotenone and in the formation of alkali-soluble products obtained by hydrogenation of various rotenone derivatives. These results have since been explained on the basis of certain secondary reactions, but the lactone theory became firmly established in the earlier stages of the investigations and caused much confusion in the speculations on the structure of rotenone and its derivatives. It was finally abandoned after it was found that all the oxygen atoms, with the exception of the one contained in the carbonyl group, are present as ether linkages.

of its derivatives. The structure for rotenone now unreservedly accepted is expressed by formula I (24, 5, 50).

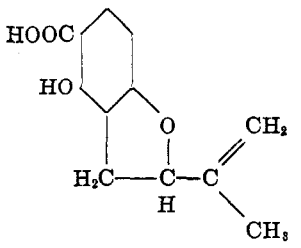


I

This formula consists of three characteristic systems,—a central dihydro-γ-pyrone (A), combined on the one hand with a dihydrobenzopyran (B), and on the other with a dihydrobenzofuran system (C). On the basis of this formula, all well-defined reactions of rotenone can be easily explained. The characteristic rotenone derivatives, which will be discussed in detail, result from reactions which are characteristic of the one or the other of these systems, and are for the most part supported by analogies with other compounds containing the same groupings.

REACTIONS INVOLVING THE DIHYDROBENZOFURAN SYSTEM

The first cleavage product obtained from rotenone was tubaic acid, the formula (II) of which has been determined by an extensive series of investigations.



II

Tubaic acid was shown by Kariyone to be an optically active monobasic phenolic acid of the formula $C_{12}H_{12}O_4$, containing an indifferent oxygen atom and one double linkage which was demonstrated by its catalytic reduction to dihydrotubaic acid (20). On fusion with alkali it is converted into the optically inactive isotubaic (rotenic) acid (42).

Tubaic, dihydro- and iso-tubaic acids when heated above their melting points lose carbon dioxide and are converted into the corresponding phenols (43, 44) from which the acids can be regenerated by the action of alkali bicarbonates (44). The phenolic hydroxyl group in the acids can be acetylated, and by means of diazomethane its methylation can be accomplished, although only with great difficulty (43).

Both dihydro- and iso-tubaic acids yield isobutyric acid on oxidation with permanganate, while tubaic acid yields only acetic acid (43, 44).

Isotubanol (roteol), the phenol corresponding to isotubaic (rotenic) acid, gives resorcinol together with isovaleric acid on drastic alkali fusion (46).

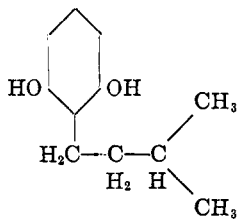
Isotubaic acid is not easily hydrogenated. It is possible, however, under energetic conditions, to add one mole of hydrogen to it forming dihydroisotubaic acid. Dihydroisotubaic acid has been shown to be a racemic mixture which can be separated into its enantiomorphs, of which the levo form is identical with dihydrotubaic acid (4, 46).

The transformations of tubaic acid so far referred to indicated that it might best be represented as a hydroxydihydrocumaroncarboxylic acid with an isopropenyl side chain (43). The resistance of the phenolic hydroxyl toward methylation indicated that it was diortho-substituted (48, 17).

By drastic hydrogenation of tubaic acid, a tetrahydrotubaic acid is obtained, together with dihydrotubaic acid (16). If the hydrogenation of tubaic acid is carried out in alkaline solution, an intermediary compound, isodihydrotubaic acid, isomeric with dihydrotubaic acid is obtained, which is easily further reduced in neutral solution to tetrahydrotubaic acid (49). Tetrahydrotubaic acid is optically inactive (16). It contains two phenolic

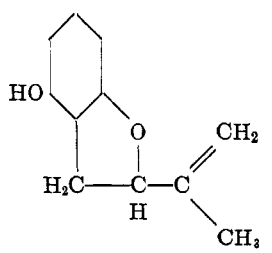
hydroxyl groups, both of which are easily acetylated. One of the acetyl groups of the diacetyl compound is easily removed by alcoholic potassium acetate solution, leaving a monoacetyl compound (17). Of the two hydroxyl groups in tetrahydrotubaic acid, only one is easily methylated (17). Tetrahydrotubaic acid is decarboxylated to a substituted dihydroxybenzene (16), which on oxidation yields isocaproic acid (50).

Owing to the properties of the hydroxyl group of tubaic acid and also with reference to certain derivatives which contain the groupings of tubaic acid in which the corresponding phenol group is free, it can be assumed that the original phenolic hydroxyl group is diortho-substituted (48, 17). Tetrahydrotubanol is therefore 2-isoamylresorcinol as represented by formula III (16, 17). This formula has lately been confirmed by synthesis (10a).



III

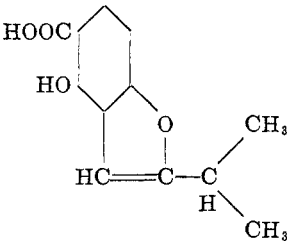
Tubanol is expressed by formula IV.



IV

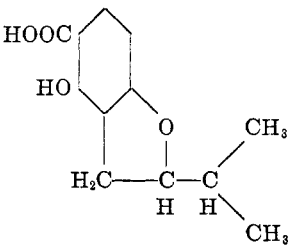
Formula II satisfactorily explains all the transformations of tubaic acid. Its isomerization is due to the migration of the double bond from the side chain into the ring, and isotubaic acid

is therefore expressed by formula V; this formula has been confirmed by synthesis (34a).



V

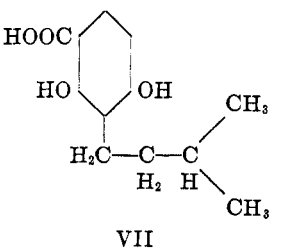
When tubaic acid (II) is reduced to dihydrotubaic acid, the double bond in the side chain is saturated, with the formation of the optically active dihydrotubaic acid of formula VI.



VI

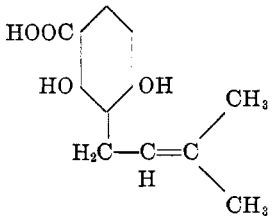
Isotubaic acid (V) is reduced to racemic dihydrotubaic acid, which can be separated into the two active forms. The levo form is identical with the natural active dihydrotubaic acid.

The hydrogenation of tubaic acid also takes place in another manner, with opening of the oxide ring involving the loss of an asymmetric center, followed by reduction of the double bond, and results in the formation of tetrahydrotubaic acid of formula VII (16, 17).



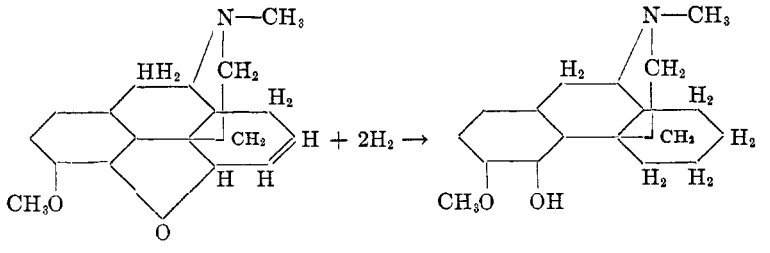
VII

If the hydrogenation is carried out in alkaline solution, the oxide ring is opened without reduction of the double bond, which probably shifts to the 2, 3-position, and the intermediary product, isodihydrotubaic acid (VIII), can be isolated (49).

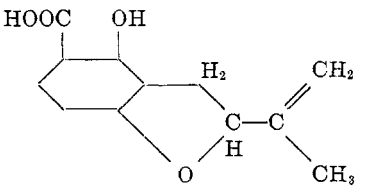


VIII

On further hydrogenation in neutral solution, isodihydrotubaic acid yields tetrahydrotubaic acid (VII). The behavior of tubaic acid on hydrogenation has a striking analogy with that of a number of codein derivatives, of which the following is an example. Desoxycodein-C of formula IX is hydrogenated to β-tetrahydrodesoxycodein (38) of formula X. The groupings involved are analogous to those present in tubaic acid (II), the formula of which may be written also as shown in formula XI.



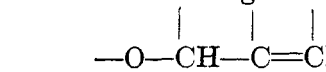
IX X



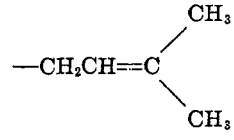
XI

On hydrogenation of both compounds the oxide ring is opened and phenolic compounds are formed.

According to the theory of Schöpf (37), the grouping concerned,



is comparable to a conjugated system, and hydrogenation takes place with the opening of the ether ring. This reaction is explained by the assumption that a 1, 4 addition of hydrogen (at —O— and C_4) first takes place, followed by the formation of a double bond at 2, 3. This double bond may be further reduced to the tetrahydro derivative, as in the case of the codein derivatives and tetrahydrotubaic acid, but remains unsaturated in isodihydrotubaic acid (VIII), which therefore contains the grouping,

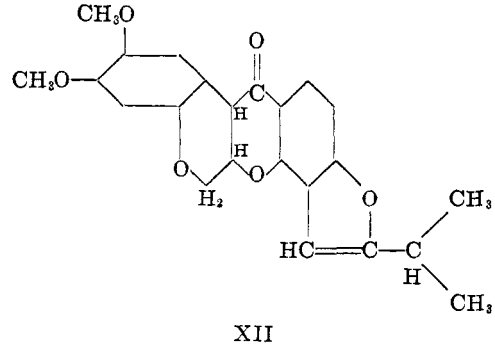


When the 2-isoamylresorcinol (III) formed by the decarboxylation of tetrahydrotubaic acid is oxidized, the resorcinol is destroyed and isocaproic acid can be isolated from the reaction products.

All these reactions, which are characteristic of the dihydrobenzofuran system of tubaic acid, find their parallel in those rotenone derivatives in which this grouping is present.

THE ISOMERIZATION OF ROTENONE AND OF THOSE OF ITS DERIVATIVES WHICH CONTAIN THE ISOPROPENYL SIDE CHAIN

When rotenone is treated with strong acids, it is converted into isorotenone (XII) (5, 42, 10).



XII

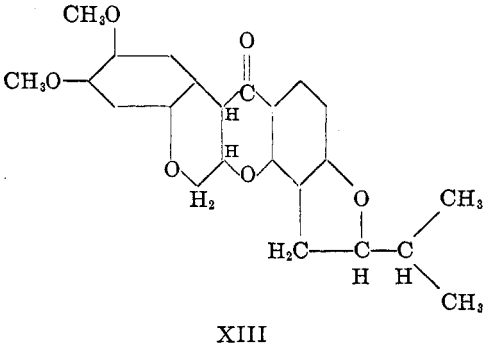
The reaction involved is the same as that which takes place when tubaic acid is converted into isotubaic (rotenic) acid. Like isotubaic acid, isorotenone is not readily reduced by catalytic hydrogenation. On cleavage with alcoholic alkali, isotubaic acid is obtained instead of tubaic acid (45, 4, 11).

All rotenone derivatives which contain the isopropenyl side chain are converted by strong acid into the corresponding iso-derivatives (4), which in turn yield isotubaic acid. Isorotenone shows all the characteristic reactions which are concerned with changes in the dihydro-γ-pyrone and dihydrobenzopyran systems. For example, isoderritol and isorotenol (27), isodehydrorotenone (29, 4), and isoderrisic acid (4) are obtained from isorotenone itself by suitable processes as well as by isomerization of the normal compounds with the unsaturated side chain (4), and isorotenonone is obtained by oxidation of isorotenone (50).

As will be shown below, two asymmetric centers are lost in the formation of the dehydro compounds and the derritols. Since another asymmetric center disappears in the formation of the iso compounds, isodehydrorotenone, isoderrisic acid (4), and isoderritol (15) are optically inactive.

HYDROGENATION PRODUCTS OF ROTENONE

When rotenone is reduced with catalytic hydrogen the main product of the reaction is dihydrorotenone (XIII) (20, 27).



XIII

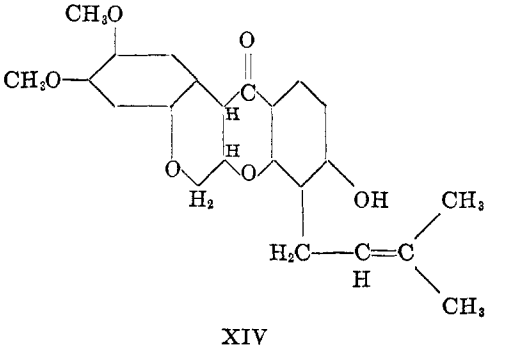
Dihydrorotenone usually melts at 216°C., but it occurs in dimorphic form, the unstable modification of which melts at 164°C. (26). It contains no double bond in the side chain and is there-

fore not isomerized by acids, but it gives all the reactions characteristic of the dihydrobenzopyran and dihydro-γ-pyrone systems.

Dihydrorotenone, and also rotenone, yield a monoacetyl derivative when treated with sodium acetate and acetic anhydride. These compounds are the enol type of acetates (41) as is shown by their behavior on hydrogenation. Acetyldihydrorotenone is reduced by catalytic hydrogenation to dihydrodesoxyrotenone (41).

The dihydro derivatives are obtained from dihydrorotenone by the same processes by which the corresponding unsaturated compounds are obtained from rotenone. Thus dihydrorotenone yields dihydroderritol, dihydrorotenol (27), and dehydrodihydrorotenone (29). All rotenone derivatives containing the unsaturated side chain yield corresponding dihydro compounds by hydrogenation.

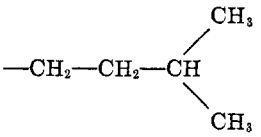
When the dihydro compounds are prepared by hydrogenation, the reaction proceeds in part with opening of the oxide ring, as in the case of tubaic acid, with the resultant loss of an asymmetric center and formation of phenolic derivatives (27, 15). The reduction takes the latter course, especially in alkaline solution. In some cases the unsaturated phenol can be isolated. Rotenone itself is thus hydrogenated in neutral solution to a mixture of dihydrorotenone and rotenonic acid (XIV) (27, 10),[2] the latter being a phenol corresponding to isodihydrotubaic acid (VIII).



XIV

[2] These phenolic derivatives were formerly thought to be acids arising from the opening of a lactone group and in some instances the term "acid" has been retained.

The double bond may be further reduced, with the formation of dihydrorotenonic acid (tetrahydrorotenone) containing the saturated side chain,

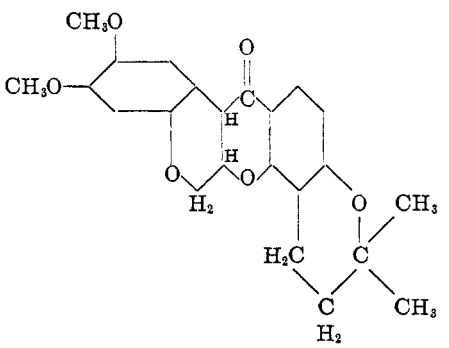


Dihydrorotenonic acid (tetrahydrorotenone) therefore differs from rotenonic acid only by having a saturated side chain.

When dihydrorotenonic acid is boiled with acetic anhydride and sodium acetate the resulting product is a diacetyl compound (41). This result is explained by the assumption that this compound, like rotenone and dihydrorotenone, reacts to form an enol acetate. One of the acetyl groups in dihydrorotenonic acid is therefore of the enol acetate type, whereas the other results from the acetylation of the phenol group. Tetrahydro derivatives of all the characteristic rotenone derivatives have been obtained by hydrogenation (16, 24, 28, 29, 31). All of these are phenols, soluble in alkali.

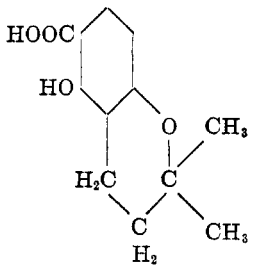
It is of special importance that with the reductive cleavage of the oxide ring of the benzofuran system an asymmetric center is lost (15). If this reductive cleavage is associated with a reaction involving the loss of the asymmetric centers of the dihydro-γ-pyrone system, the resulting compounds are inactive (4, 15). Tetrahydromethylderritol (methyldihydroderritolic acid) (XXVI) and tetrahydrodehydrorotenone (dehydrodihydrorotenonic acid) (XXXII) are, for example, inactive (15).

Rotenonic acid (XIV) undergoes a rearrangement when treated with sulfuric acid whereby it is converted into β-dihydrorotenone (XV), (9, 10), containing the chroman in place of the dihydrobenzofuran system.



XV

This reaction is in a measure comparable to the conversion of an unsaturated acid into a saturated lactone and involves a ring closure with disappearance of the phenol group and the double bond. β-Dihydrorotenone exhibits those reactions characteristic of the dihydro-γ-pyrone system and is cleaved by alkali, with the formation of β-dihydrotubaic acid of the probable formula XVI (9, 10, 5).



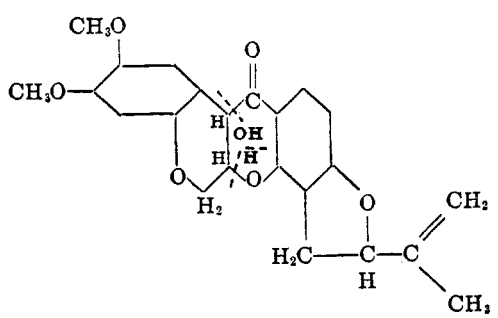
XVI

The corresponding dehydro derivative has been prepared from β-dihydrorotenone and is hydrolyzed by alkali to β-dihydroderrisic acid, which in turn has been oxidized to derric acid (9).

Derrisic acid is also hydrogenated to the corresponding tetrahydro derivative, which, owing to its importance in connection with dehydrorotenone, will be discussed more fully under a separate heading.

REACTIONS INVOLVING THE DIHYDROBENZO-γ-PYRONE SYSTEM

The dihydrobenzo-γ-pyrone ring is responsible for the instability of rotenone, and those of its derivatives which contain this grouping, toward alkali. Those derivatives in which this grouping is absent are much more stable in alkaline solution. By the action of alcoholic alkali rotenone is quickly decomposed, with the formation of large quantities of uncrystallizable resins. From these a small yield of tubaic acid is obtained (20, 42, 44, 12).



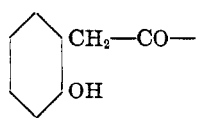
XVII

It seems very probable that the first point of attack involves the hydrolysis of the oxidic linkage of the dihydrobenzo-γ-pyrone ring (4). Under ordinary conditions in the presence of air this reaction is followed to a certain extent by cleavage at the carbonyl group, with the formation of tubaic acid as shown in formula XVII.

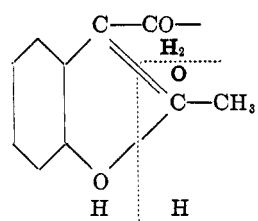
Derritol

When the alkaline cleavage is carried out under reducing conditions, as in the presence of zinc, the main products are derritol and rotenol (2, 3). These derivatives have proved to be of special importance in determining the structure of rotenone.

The empirical formula ($C_{21}H_{22}O_6$) for derritol as determined by Butenandt (3) differs from that of rotenone in that it contains two carbon atoms less than the parent substance. It is separated from the rotenol, which is simultaneously formed in the process, by means of alkali, in which the rotenol is nearly insoluble. The corresponding iso- and dihydro-derritols were later prepared from iso- and dihydro-rotenone by the same process. Isoderritol is optically inactive, whereas the other two are active (15). Derritol contains the two methoxyl groups and the carbonyl group originally present in rotenone. The presence of a phenolic hydroxyl group was indicated by its solubility in alkali as well as by the color reaction with ferric chloride. The presence of a second hydroxyl group was indicated by the Zerewitinoff method (3). From these facts it was suggested by Butenandt that derritol possibly contained the grouping XVIII, resulting from reduction and hydrolysis of the grouping XIX (3).

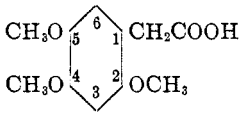


XVIII



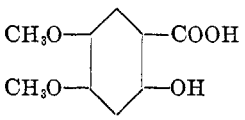
XIX

Of the two hydroxyl groups of derritol, only one is easily methylated. The resulting derritol monomethyl ether (XXV) (28) is hydrogenated to the alkali-soluble tetrahydromethylderritol (XXVI) (28), which is oxidized by hydrogen peroxide to a trimethoxyphenylacetic acid (39). The trimethoxyphenylacetic acid has been oxidized to its next lower homologue, which is identical with asaronic acid or 2, 4, 5-trimethoxybenzoic acid (40). The structure of the 2, 4, 5-trimethoxyphenylacetic acid, (homoasaronic acid) (XX) has also been established by synthesis (50).



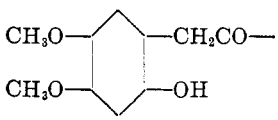
XX

When derritol itself is oxidized with permanganate in acetone solution, 2-hydroxy-4, 5-dimethoxybenzoic acid (40) is obtained, the structure of which (XXI) has been established by Clark (7) as well as confirmed by synthesis (50, 35).



XXI

From these facts it follows that derritol contains the grouping XXII.

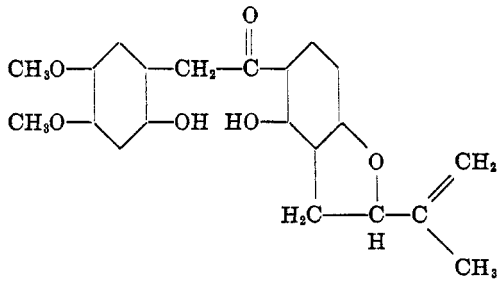


XXII

By alkali fusion derritol yields isotubaic acid[3] (13), and by permanganate oxidation, tubaic acid (48). Isotubaic and dihydrotubaic acids are likewise obtained from iso- and dihydro-derritols

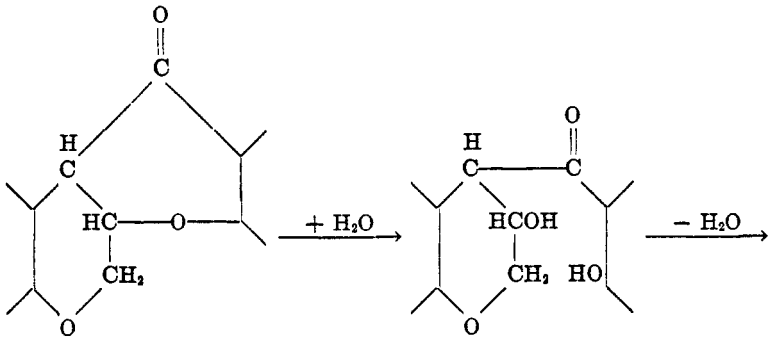
[3] Under the conditions of alkali fusion the tubaic acid grouping is converted into the isotubaic acid structure.

(13). The foregoing facts establish the formula for derritol as XXIII.

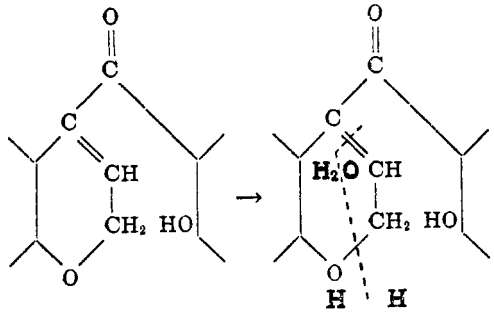


XXIII

The mechanism of the reactions leading to the formation of derritol is best explained by the following series of reactions (24):

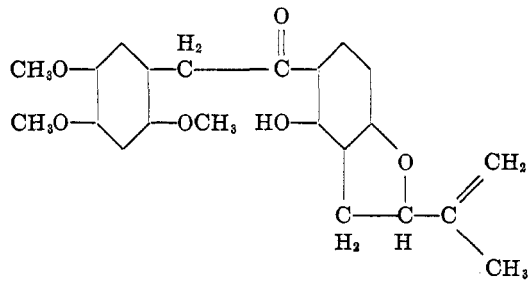


Rotenone XXIV



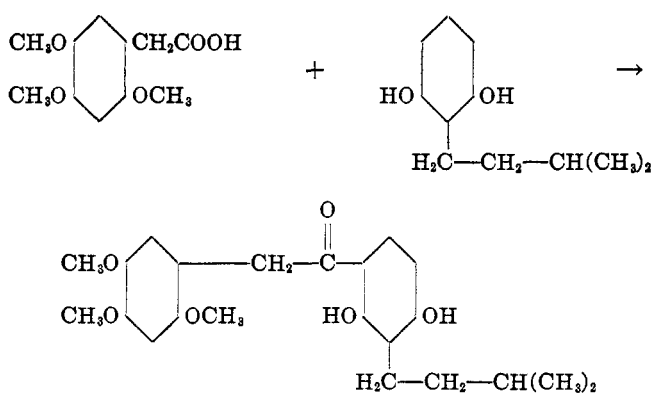
XXIV-A Derritol

Derritol methyl ether is therefore represented by formula XXV.



XXV

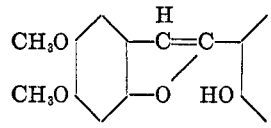
The hydroxyl group attached to the tubaic acid part of the derritol molecule is resistant to methylation and is of such weak acidic properties that its hydrogen is not replaced by alkali metals. Consequently, derritol methyl ether (XXV) is not soluble in alkali, although it gives a color reaction with ferric chloride. Derritol methyl ether is oxidized by hydrogen peroxide at the carbonyl group to homoasaronic acid.[4] Tetrahydromethylderritol (XXVI) has been synthesized from tetrahydrotubanol (III) and homoasaronic acid (XX) by condensation with zinc chloride (50).



XXVI

[4] All aromatic aldehydes and ketones having a phenolic hydroxyl group in the ortho or para position are oxidized by hydrogen peroxide to polyphenols without the formation of a substituted benzoic acid (17).

The derritols are easily dehydrated (3, 41) and the resulting anhydroderritols which contain the grouping XXVII are also

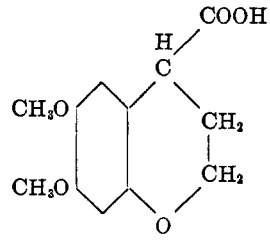


XXVII

insoluble in alkali, but give the ferric chloride color reaction and yield monoacetyl derivatives.

Rotenol

Rotenol is obtained, together with derritol, by zinc alkali reduction of rotenone (3), and corresponding compounds are obtained from iso- and dihydro-rotenone (27). It was at first supposed that rotenol was the alcohol corresponding to rotenone (3) because no ketone derivatives of rotenol could be obtained by the usual methods. Evidence for the presence of the carbonyl group was furnished by the fact that isorotenol, which differs from rotenol only in the arrangement of the benzofuran system, was reduced by Clemmenson's method to desoxyisorotenol (14). Later Takei succeeded in obtaining an oxime from rotenol (49). By peroxide oxidation rotenol, or the corresponding tetrahydrorotenol (dihydrorotenolic acid), yields netoric acid $C_{12}H_{14}O_6$ (5, 39), in all probability to be represented by the formula XXVIII (25).



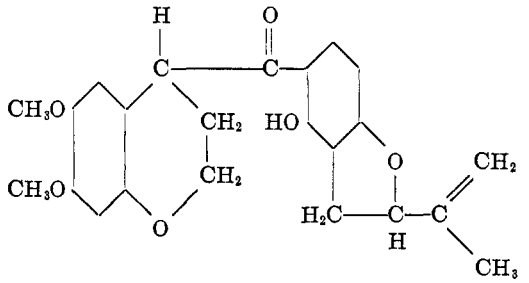
XXVIII

Rotenol yields isotubaic acid on alkali fusion in much larger quantities than any other rotenone derivative (13). Both derri-

tol methyl ether and rotenol give all the characteristic reactions (isomerization to iso derivatives, cleavage of the oxide ring on hydrogenation, with loss of an asymmetric center and formation of a phenolic hydroxyl group and reduction to dihydro and tetrahydro derivatives) of those rotenone derivatives which are concerned with the dihydrobenzofuran system.

By the action of alkaline ferricyanide, a dehydrorotenol (14, 10, 25) is obtained which is isomeric with rotenone, and which is easily reconverted into rotenol by zinc alkali reduction. The structure of dehydrorotenol is as yet unexplained, but it seems to be unrelated to dehydrorotenone.

Rotenol results from the reduction of the unsaturated intermediary product (XXIV-A), which is formed with loss of an asymmetric center and is represented by the formula XXIX.



XXIX

Corresponding formulas with suitable arrangements in the benzofuran nucleus apply to its derivatives, iso-, dihydro-, and tetrahydro-rotenol. Isorotenol and tetrahydrorotenol, which have no other asymmetric center, are therefore racemic mixtures.

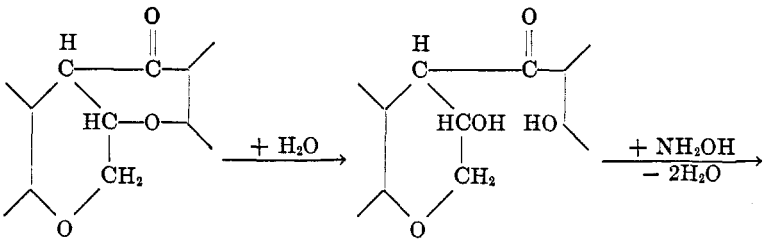
ISOMERIC CARBONYL DERIVATIVES OF ROTENONE

Two types of carbonyl derivatives are obtained from rotenone. When its oxime or hydrazone is prepared in acid solution the normal derivatives are obtained. If, however, the reaction is carried out in alkaline solution, isomeric compounds result which are soluble in alkali and exhibit the properties of phenols (3).

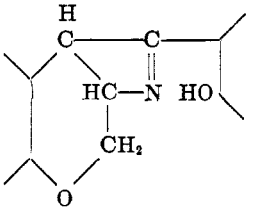
The formation of these phenolic carbonyl derivatives is best

explained with the assumption that the oxidic linkage of the dihydrobenzo-γ-pyrone system is first hydrolyzed, as is represented by the first step in the formation of derritol and rotenol. The carbonyl derivative of the intermediary compound of formula XXIV then rearranges, with loss of one mole of water to form the phenolic isocarbonyl derivative (XXX).

The reactions resulting in the formation of rotenone isoxime may be illustrated as follows:



Rotenone XXIV

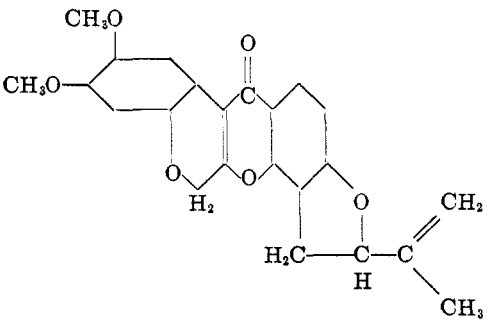


XXX

Dehydrorotenone

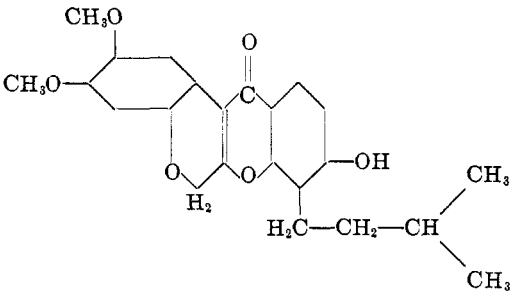
A number of mild oxidizing agents convert rotenone into dehydrorotenone with the loss of two hydrogen atoms from the dihydro-γ-pyrone system, and corresponding dehydro compounds are obtained from all derivatives which contain the dihydro-γ-pyrone system, for example, from isorotenone (XII), dihydrorotenone (XIII), and β-dihydrorotenone (XV).

For reasons which will be presented dehydrorotenone is expressed by formula XXXI (24, 5, 50, 36).



XXXI

Dehydrorotenone is optically active, but isodehydrorotenone is inactive (3). Since it has already been demonstrated that an asymmetric center is lost in the process of isomerization, it is apparent that the remaining asymmetric centers are lost in the formation of the dehydro compounds. The combination of the two reactions leads to an optically inactive compound (3). Similarly the catalytic reduction of dehydrorotenone with opening of the oxidic linkage of the dihydrobenzofuran grouping, a reaction which also involves the loss of a center of optical activity, leads to an optically inactive compound, dehydrodihydrorotenonic acid[5] (tetrahydrodehydrorotenone) (XXXII) (15).



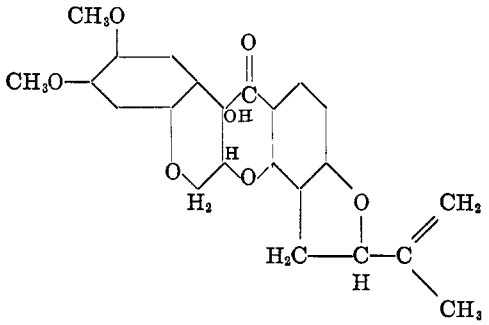
XXXII

The most convenient method for preparing the dehydro compounds is by the action of iodine and alkali acetate on an alcoholic

[5] It has not been possible by any means to reduce the double bond in the γ-pyrone system of dehydrorotenone.

solution of rotenone, iso- or dihydro-rotenone (3, 27). Some of the dehydro compound is obtained directly, but the main product of the reaction consists of the acetate of a hydroxy derivative (27). By this process, rotenone yields acetylrotenolone. Rotenolone, obtained on saponification of the acetyl compound, is represented by the formula $C_{23}H_{22}O_7$, and is to be regarded as a hydroxyrotenone. Its formation is explained by a process of iodine substitution at one of the labile hydrogen atoms of the dihydro-γ-pyrone system, followed by reaction of the iodo compound with the alkali acetate.

Rotenolone, which is represented by the formula XXXIII,[6] is easily dehydrated by alcoholic sulfuric acid to dehydrorotenone (XXXI) (27).

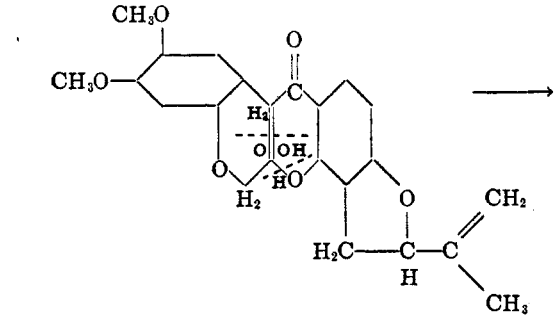


XXXIII

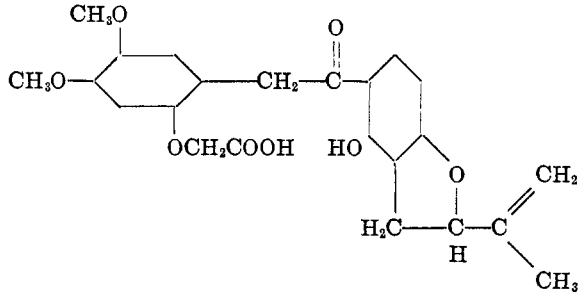
Corresponding formulas apply to iso-, dihydro- (27), and β-dihydrorotenolone (9), all of which have been obtained by the same process.

Dehydrorotenone is converted by alcoholic alkali, or zinc and alkali with addition of two molecules of water, into derrisic acid of formula XXXIV (3, 24).

[6] It is possible that the hydroxyl group is on the other asymmetric carbon atom of the dihydro-γ-pyrone ring and there also exists the possibility of *cis-trans* isomerism. Either of these theories could explain the existence of the isomeric rotenolone derivatives which have been observed (31).



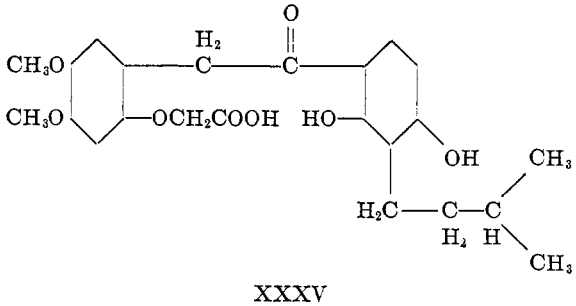
XXXI



XXXIV

Derrisic acid stands in close relation to derritol (XXIII). Its ethyl ester is obtained by substitution of the $CH_2COOC_2H_5$ group on the reactive phenol hydroxyl (25). It has been shown to contain a free phenol group which gives a color reaction with ferric chloride, and which may be acetylated (3). Iso- and dihydroderrisic acids are obtained by the same reaction from iso- and dihydro-derritol.

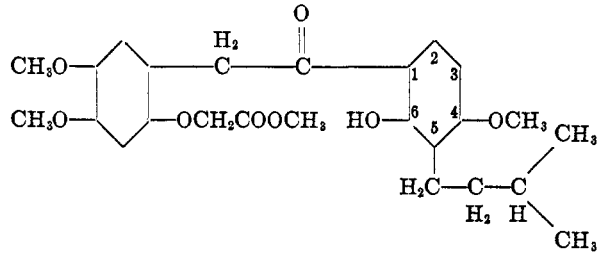
Like all rotenone derivatives containing the dihydrobenzo-γ-furan grouping with the unsaturated side chain, derrisic acid is hydrogenated to tetrahydroderrisic acid of the formula XXXV (24).



XXXV

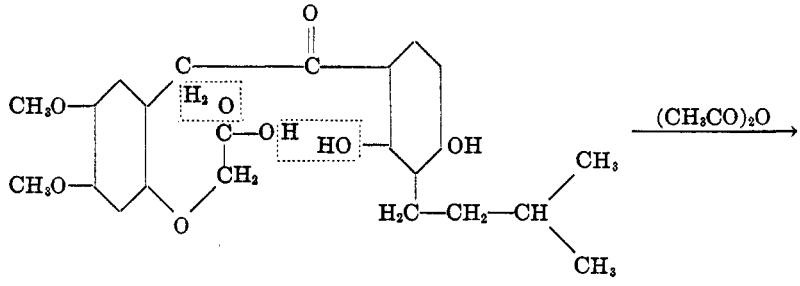
The same compound is also obtained by alkaline hydrolysis of dehydrodihydrorotenonic acid (tetrahydrodehydrorotenone) (XXXII) (31, 24), the reaction being the same as that involved in the formation of derrisic acid from dehydrorotenone.[7]

Tetrahydroderrisic acid is methylated to the methyl ester of monomethyltetrahydroderrisic acid (XXXVI) which is alkali-insoluble (24).[8]



XXXVI

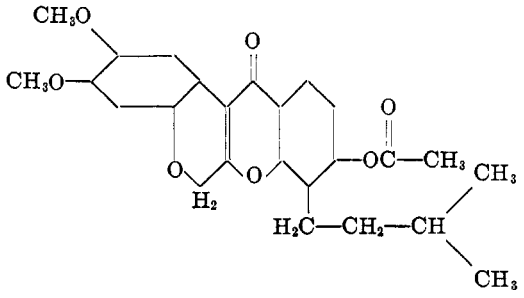
By the action of acetic anhydride and anhydrous sodium acetate, tetrahydroderrisic acid (XXXV) is converted by dehydration and acetylation into the monoacetyl derivative of dehydrodihydrorotenonic acid (tetrahydrodehydrorotenone) (XXXVII) (24), from which the acetyl group is easily removed.



XXXV

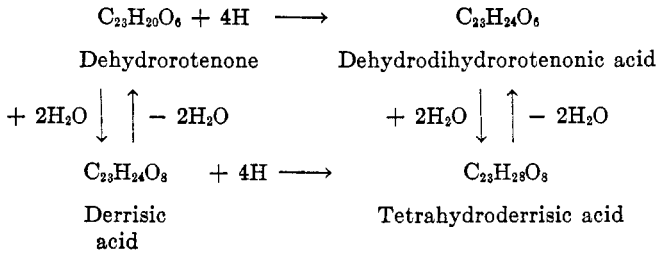
[7] In this as well as in other instances the reductive cleavage of the oxidic linkage of the dihydrobenzofuran system can be effected either before or after some other reaction has been performed, and the same end product is obtained in each case.

[8] All rotenone derivatives which contain only one diortho-substituted phenolic group (position 6) are difficultly soluble in alkali and are not easily methylated. For example, rotenol and derritol methyl ether.



XXXVII

By the same treatment, derrisic acid (XXXIV) is converted into dehydrorotenone (XXXI), the reaction being the reverse of that involved in the conversion of dehydrorotenone into derrisic acid (24). These relations are expressed by the formulas in the following chart:

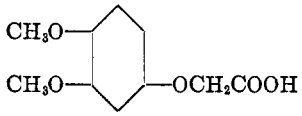


The methyl ester of methyltetrahydroderrisic acid (XXXVI) does not undergo ring closure when treated with acetic anhydride and sodium acetate but is simply converted into the 6-acetyl derivative (24). The free acid is, however, dehydrated by the same treatment, yielding 4-methyldehydrodihydrorotenonic acid (4-methyltetrahydrodehydrorotenone), which is identical with the product obtained on methylation of dehydrodihydrorotenonic acid (XXXII) (24).

The structure of derrisic acid has also been determined independently of its relation to derritol.

On oxidation of derrisic acid with hydrogen peroxide in alkaline solution, derric acid, of the formula $C_{12}H_{14}O_7$, a dibasic acid containing two methoxyl groups and one unreactive oxygen atom, is

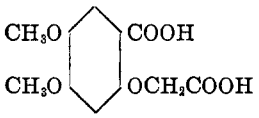
obtained (29). Permanganate oxidation converts derric acid into its next lower homologue, risic acid, of the formula $C_{11}H_{12}O_7$ (30). Risic acid melts with evolution of gas, and on continued heating is converted with the loss of one carboxyl group into the monobasic decarboxyrisic acid of the formula $C_{10}H_{12}O_5$ (22, 47). The structure of decarboxyrisic acid has been established as XXXVIII by its synthesis from 3, 4-dimethoxyphenol, which process involved the substitution of the CH_2COOH group on the phenol hydroxyl by means of iodoacetic ester (22).



XXXVIII

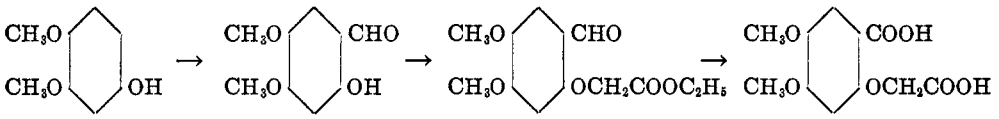
On treatment with phosphorus pentachloride, decarboxyrisic acid yields a monochloro acid of the formula $C_{10}H_{11}O_5 \cdot Cl$ (22).

The formula for risic acid has been established as XXXIX (22).

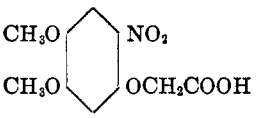


XXXIX

Risic acid has been synthesized from 2-hydroxy-4, 5-dimethoxybenzoic acid (XXI) (50) by the same process as that employed for the synthesis of decarboxyrisic acid. It has also been prepared synthetically by the following steps (36).

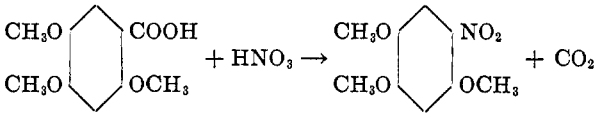


Risic acid is converted by dilute nitric acid into nitrodecarboxyrisic acid (XL) (22).

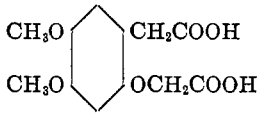


XL

This reaction is analogous to the behavior of asaronic acid, which is converted by the same reagent into 2, 4, 5-trimethoxynitrobenzene.

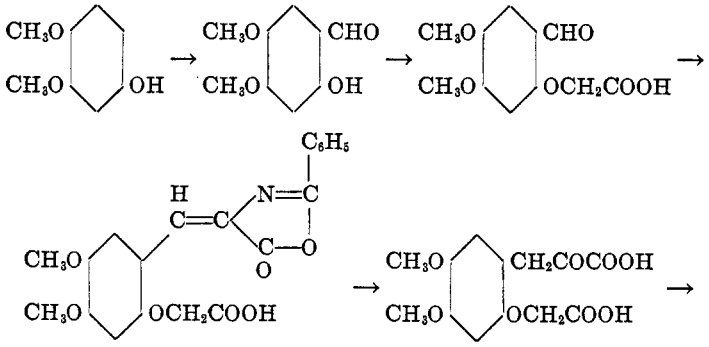


Risic acid is obtained directly from dehydrodihydrorotenonic acid (XXXII) by peroxide oxidation (31), the oxidation taking place at the double bond as well as at the carbonyl group. The formula for derric acid (XLI) can be deduced from those of its degradation products, reasoning from the fact that homoasaronic acid (XX) is obtained from derritol methyl ether (XXV) (22).



XLI

Derric acid has been synthesized through the following series of intermediary compounds (36):



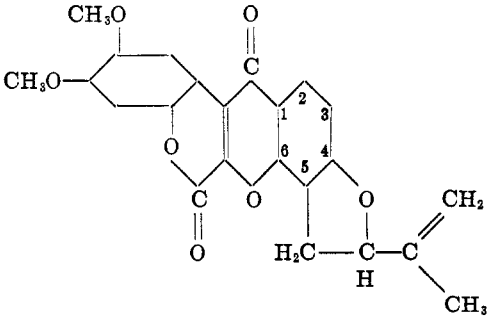
XLI

With the structure of derrisic acid and its relation to dehydrorotenone established, the nature of the groupings which compose the skeleton of the rotenone molecule could be deduced.

REACTIONS INVOLVING THE DIHYDROBENZOPYRAN SYSTEM

Rotenone is oxidized by chromic acid (42) or by nitrous acid (3) to rotenonone, a yellow compound of the formula $C_{23}H_{18}O_7$ (29); analogous compounds are obtained in the same manner from iso- (50), dihydro- (29), and β-dihydro-rotenone (9), as well as from dihydrorotenonic acid (29). It is apparent that the first step of this oxidation process consists in the formation of the dehydro derivatives, because rotenonone and its analogues are also obtained from the corresponding dehydro compounds (29).

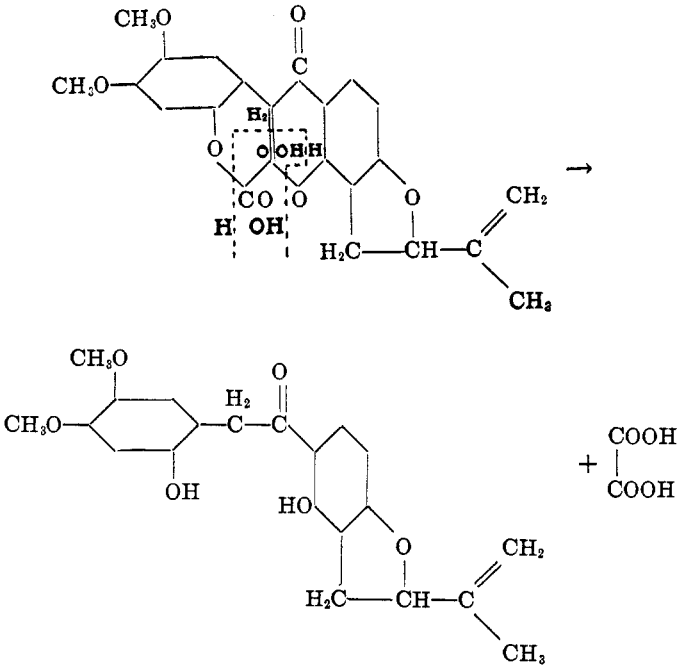
Rotenonone was at first supposed to be a 1, 2-diketone formed by the oxidation of a methylene group adjacent to a carbonyl group (3). From the formula (XXXI) for dehydrorotenone, it is apparent that oxidation of the methylene group in the benzopyran system (B, formula I) to a carbonyl group is the only plausible explanation for the formation of rotenonone. This change from a benzopyran to a benzo-α-pyrone system results in the formation of a coumarin derivative and rotenonone is, therefore, to be represented by the formula XLII (5, 50, 23).



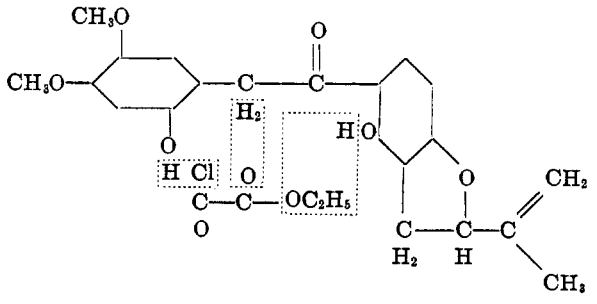
XLII

Rotenonone and its analogues are therefore lactones and as such are hydrolyzed to hydroxy acids (42, 29). Rotenonone itself is converted by the action of alkali into rotenononic acid of the

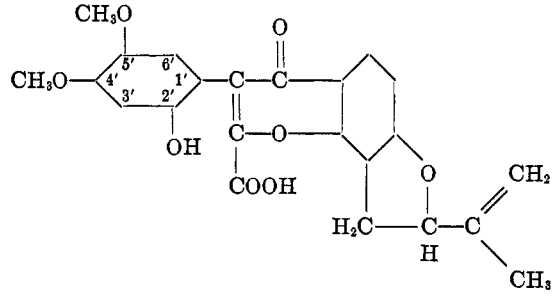
formula $C_{23}H_{20}O_8$ (29). By energetic alkaline hydrolysis, rotenonone or rotenononic acid is further cleaved with the formation of derritol and oxalic acid (50, 5, 23).



By the reverse process, rotenonone has been synthesized by the action of chloroxalyl ethyl ester on derritol (23).



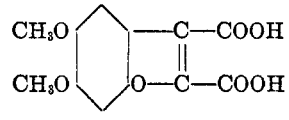
It was first supposed that rotenononic acid was the primary product resulting from simple hydrolysis of the coumarin ring present in rotenonone, to be expressed by the formula XLIII.



XLIII

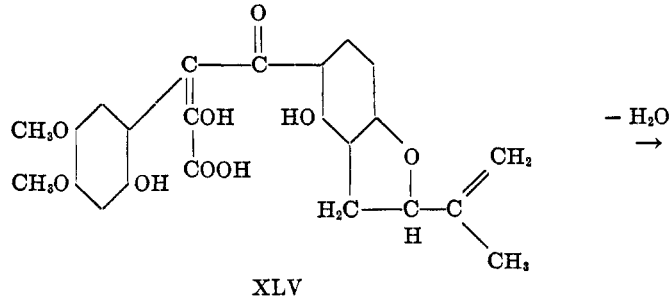
This formula however fails to explain certain experimental facts.

By oxidation of rotenononic acid, together with tubaic acid, the dibasic abutic acid, $C_{12}H_{10}O_7$, is obtained. Abutic acid contains two methoxyl groups and an indifferent oxygen atom and is to be expressed by formula XLIV (50).

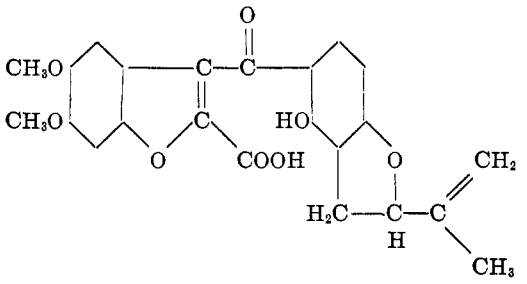


XLIV

The formation of abutic acid is accounted for by the theory of Takei (50), that the primary product of hydrolysis of rotenonone (XLII) is further hydrolyzed to the intermediary compound XLV. A new ring closure then occurs as indicated below. Formula XLVI should, therefore, be assigned to rotenononic acid (50).



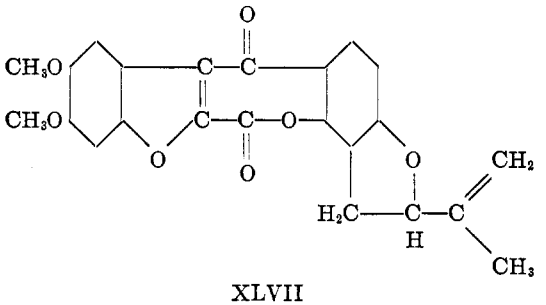
XLV



XLVI

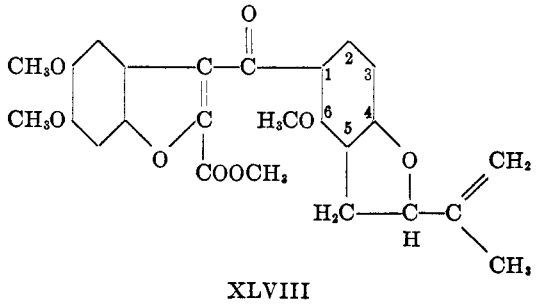
Abutic acid (XLIV) is obtained by oxidation of XLVI.

Rotenononic acid (XLVI), in acid solution, changes over into an isomer of rotenonone, β-rotenonone, of the formula XLVII.



XLVII

This β-rotenonone rearranges in weak alkaline solution through the intermediary compound XLV to rotenonone (XLII) (50). Rotenononic acid is easily methylated by dimethyl sulfate or diazomethane to its methyl ether methyl ester (50, 23), which is represented by formula XLVIII.



XLVIII

The corresponding acid is obtained by saponification of the ester (23). The methyl ester of methylrotenononic acid is hydrogenated to the phenolic alkali-soluble tetrahydro derivative with the opening of the oxide ring in the dihydrobenzofuran system (23).

It is remarkable that the phenolic hydroxyl group of rotenononic acid in position 6 is methylated by dimethyl sulfate, because no other derivatives, such as rotenol, derritol methyl ether, and derrisic acid, which have a free hydroxyl in this position, can be methylated by this reagent. It appears, however, that the methoxyl group in position 6 is easily saponified by alkali. The methyl ether of rotenononic acid yields derritol by energetic alkaline hydrolysis and is partly reconverted by milder alkaline treatment into rotenonone. These facts strongly support the formula XLVI proposed by Takei for rotenononic acid. On the other hand, formula XLIII for rotenononic acid is excluded, since its methyl ether, which would have a methoxyl group in position 2′, would yield by alkaline hydrolysis, derritol methyl ether (XXV), which is itself unaffected by prolonged boiling with strong alkali.

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