3. At *P*H 3.25 to 3.35 the temperature coefficient u = 23,000, while at *P*H 3.55, u = 24,000.

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

ROTENONE. IV. CONSTITUTION OF ROTENONE

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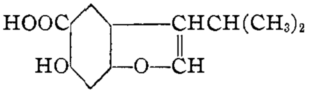
Up to the present it has not seemed advisable to propose a constitutional formula for rotenone. This has not been because data were lacking, for a very large number of rotenone derivatives have been prepared and several unusual reactions peculiar to rotenone have been observed, but until the recent publication of Takei's[1] formula for tubaic and rotenic acids, the particular key fact had been missing. About a year ago Butenandt[2] published an article in which he stated that a constitutional formula for rotenone must fulfil the following requirements.

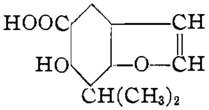
"It must explain: (1) the optical activity; (2) the indifference toward methylmagnesium iodide, ferric chloride, diazomethane and acetic anhydride; (3) the reduction of Fehling's solution; (4) the formation of two groups of structurally different oximes and hydrazones; (5) the formation of dehydrorotenone by loss of two hydrogen atoms and the conversion of this compound to a monocarboxylic acid by addition of two moles of water; (6) the cleavage of rotenone to derritol, a yellow phenol containing two atoms of carbon less than rotenone; (7) the cleavage of rotenone to tubaic acid; (8) the formation of a monocarboxylic acid $C_{23}H_{26}O_6$ by hydrogenation in ammoniacal solution."

At the time of Butenandt's publication the structure of tubaic acid had not been determined, although Takei[3] had tentatively proposed the formula

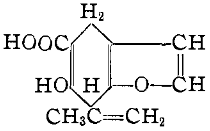


for rotenic acid. Derric acid,[4] which corresponds to the half of the rotenone molecule that carries the methoxyl groups, had not yet been isolated.

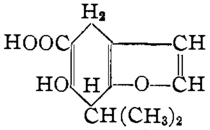
In his most recent article, Takei[1] has proposed the following formulas



Rotenic acid



Tubaic acid



Dihydrotubaic acid

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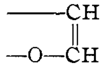
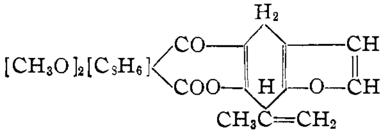
[1] Takei, *Bull. Inst. Phys. Chem. Res.*, **8**, 519 (1929).

[2] Butenandt, *Ann.*, **464**, 270 (1928).

[3] Takei, *Ber.*, **61**, 2943 (1928).

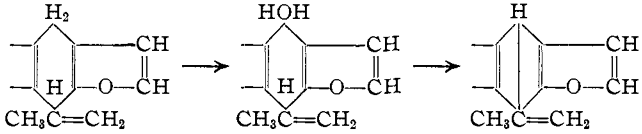
[4] LaForge and Smith, THIS JOURNAL, **52**, 1091 (1930).

He gives very good reasons in support of these formulas, at least in so far as the nature of the nucleus contained in tubaic acid is concerned. The peculiar nature of the nucleus postulated is sufficient to explain the known reactions of tubaic, dihydrotubaic and rotenic acids. Not only does it explain the reactions of these acids but, taking into consideration the formation and the nature of derric acid, a formula for the entire rotenone molecule may be proposed which fulfils all of the conditions imposed by Butenandt, without a single known discordant fact, as well as explains certain new facts which we ourselves have observed. In this formula several details concerning the structure of the part of the molecule which gives derric acid still remain to be worked out and, as far as we know, the positions of attachment of the grouping  $\begin{matrix}\text{——CH}\\ \Vert\\ \text{—O—CH}\end{matrix}$ in tubaic acid are still uncertain.



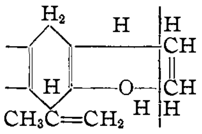
Rotenone

A compound of this formula would have the following characteristics: (1) it would be optically active; (2) it would contain no hydroxyl group to react with methylmagnesium iodide, ferric chloride, acetic anhydride, etc.; (3) it would have a ketone group and would be expected to reduce Fehling's solution; (4) the formation of the structurally different oximes and hydrazones would be expected to take place by the opening of the lactone ring with formation of a phenol group and a carboxyl group, the latter reacting to form a new ring system, as suggested by Butenandt himself;[2] (5) we have already discussed the formation of dehydrorotenone in a previous publication. It may be illustrated as follows:

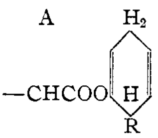


Rotenone Rotenolone Dehydrorotenone

(6) The cleavage of rotenone to derritol is best explained by the loss of the side ring from the nucleus by reduction in the manner indicated, although it seems strange that the double bond in the furan ring is not reduced by catalytic hydrogenation. However, this does not happen either with rotenone or with tubaic acid, and the fact must be due to the peculiar nature of the nucleus to which it is attached. (7) The cleavage of rotenone to tubaic acid is explained by the opening of the lactone



ring and hydrolysis or oxidation of the molecule at the carbonyl group. (8) The formation of an acid $C_{23}H_{26}O_6$ by catalytic reduction seems to be without analogy. The acid obtained by Butenandt is in all probability identical with dihydrorotenonic acid of this formula, which we have described in a previous article. Since many rotenone derivatives give analogous acids on hydrogenation, it will probably be found that as a rule any lactone containing the grouping A will react in a similar manner and give an acid on hydrogenation. In addition to the requirements postulated by Butenandt, all of which are fulfilled by the formula given by us, the derivatives of isorotenone still remain to be accounted for. These compounds are now being investigated.



Isorotenone is optically active but apparently does not contain a double bond easily reduced by hydrogen. It is easily obtained from rotenone by addition of hydrochloric acid to form rotenone hydrochloride, which in turn gives isorotenone with loss of hydrochloric acid. In a previous article[5] we have suggested that isorotenone does not contain a double bond but a ring structure instead. It seems likely that the iso-allyl group in the side chain has been converted into a trimethylene ring. Isorotenone gives isorotenol and isoderritol as well as dehydroisorotenone and dehydroisorotenonone, and has shown the typical reactions of rotenone in all our experiments, but further work on this derivative is necessary. It is to be expected that on energetic hydrogenation it would give isorotenonic acid, but not dihydro-isorotenonic acid. Dihydrorotenone should not give dihydro-isorotenone on boiling with sulfuric acid. Isorotenone should give isotubaic acid but, unlike tubaic acid, isotubaic acid on fusion with potassium hydroxide would probably not yield isorotenic acid. In other respects isorotenic acid should resemble tubaic acid, giving a phenol[6] with loss of the carboxyl group, and should exhibit similar color reactions. We are now investigating these points as well as the constitution of derric acid.

Summary

The typical reactions of rotenone are explained by a formula based on Takei's theory of the structures of rotenic, tubaic and dihydrotubaic acids, together with the composition and properties of derric acid.

The rotenone molecule is shown to consist of two parts joined together by a lactone and a ketone linkage. Rotenic acid is formed from one part, derric acid from the other.

WASHINGTON, D. C.

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[5] LaForge and Smith, THIS JOURNAL, **51**, 2576 (1929).

[6] It is unfortunate that Takei has used the word "rotenol" to designate the phenol derived from rotenic acid because this word had already been used by Butenandt to designate another compound.