[Contribution from the Insecticide Division, Bureau of Chemistry and Soils]

ROTENONE. VII. THE STRUCTURE OF TUBANOL AND TUBAIC ACID

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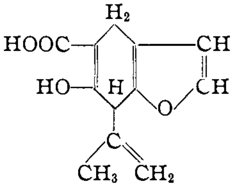
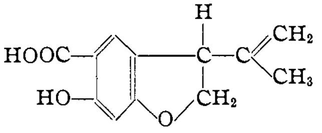
Tubaic acid, which corresponds to about half the rotenone molecule, is obtained from rotenone by the action of alcoholic potash. In recent articles, Takei, Koide and Miyajima[1] have proposed the tentative structural formulas I and II for this acid.



I

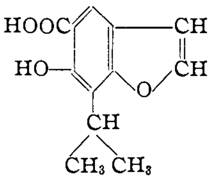


II

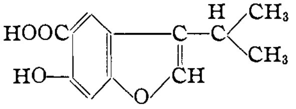
Butenandt and Hildebrandt[2] in a recent paper have also advanced arguments in favor of formula II.

In their latest communication[3] the Japanese investigators seem to prefer formula I, probably because an attempted synthesis[4] of a substance having the structure II did not meet with success. They state, however, that the position of the isoallyl (isopropylene) group may also be in the furan ring in which case this ring is hydrogenated.

Tubaic acid is converted by fusion with potassium hydroxide into an isomeric compound called rotenic acid for which Takei[1] has advanced the structural formulas III and IV. In formula IV also the isopropyl group is in the furan ring. Rotenic acid can also be prepared by fusing rotenone with solid potassium hydroxide, by dissolving tubaic acid in concentrated sulfuric acid and diluting the resulting solution with water, or by converting rotenone into isorotenone and then refluxing this compound with alcoholic potassium hydroxide solution.



III



IV

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[1] S. Takei and S. Miyajima, *Bull. Inst. Phys. Chem. Res.*, [8] **6**, 61 (1929); S. Takei and M. Koide, *ibid.*, [8] **6**, 64 (1929).

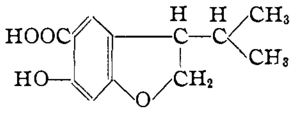
[2] A. Butenandt and F. Hildebrandt, *Ann.*, **477**, 245 (1930).

[3] S. Takei and M. Koide, *Ber.*, **62**, 3030 (1929).

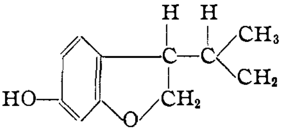
[4] Takei and Koide, *Bull. Inst. Phys. Chem. Res.*, [8] **6**, 64 (1929).

Since rotenic acid can be obtained on isomerization of tubaic acid or from isorotenone, the change which takes place is the same in both cases. The difficulty with which isorotenone and rotenic acid are reduced catalytically leads to the conclusion that the isomerization is due to the shifting of a double bond, the mechanism of which is illustrated in the structures shown above.

A recent paper by Butenandt and Hildebrandt[2] presents some interesting experimental results on rotenone and its derivatives. They conclude from their data that structure II explains the properties of tubaic acid better than does structure I and that IV represents the structure of rotenic acid. They base their conclusion principally on the fact that they have succeeded in reducing rotenic acid to a dihydro derivative, V, and in resolving this compound into its enantiomorphs,[5] thus excluding the structural formula I for tubaic acid and III for rotenic acid since in these structures the dihydrorotenic acid would not possess an asymmetric carbon atom. Butenandt and Hildebrandt, probably inadvertently, have overlooked the fact that Takei has suggested that the isoallyl (isopropylene) group might also be in the furan ring.



V



VI

On being heated to 190–200° tubaic and rotenic acids give off carbon dioxide, and neutral substances result which are considered to be phenols by Takei and by Butenandt and Hildebrandt. Takei has named the compound derived from tubaic acid by the elimination of carbon dioxide tubanol and the corresponding compound from rotenic acid rotenol. The name rotenol had already been proposed by Butenandt[6] for the reduction product obtained by the action of zinc and potassium hydroxide on rotenone. It is very desirable that this original name be retained for Butenandt's product, but in this paper, in order to avoid confusion, we shall use the term "rotenol" to designate the compound obtained from rotenic acid. A new name for this compound is desirable.

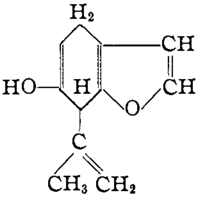
Tubaic acid in alcoholic solution gives a violet color with ferric chloride, and rotenic acid produces an intensely blue color with this reagent. *Tubanol does not give a color with ferric chloride* whereas "rotenol" gives a violet-red color.[1]

Takei has proposed the structural formulas VII and VIII for tubanol

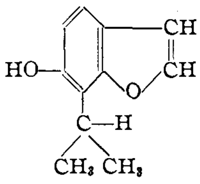
[5] Butenandt and Hildebrandt do not claim to have resolved the acid to its maximum nor has the dextro enantiomorph been resolved as much as the levo. The important point which has been established is that the compound can be resolved.

[6] A. Butenandt, *Ann.*, **464**, 253 (1928).

and "rotenol," respectively. As in the case of tubaic and rotenic acids, the isoallyl and isopropyl groups may also be in the furan ring. The results of Butenandt and Hildebrandt, however, limit the position of the isoallyl and isopropyl groups to the furan ring.



VII



VIII

A substance having the structure of tubanol, VII, would be expected to give a color with ferric chloride, particularly since "rotenol," for which the structure VIII is advanced, produces a color. It is, of course, possible for the hydroxyl group to occupy one of four positions in the benzene ring if the side chain is in the furan ring. A compound, 2-methyl-5-hydroxycoumarone, which may be regarded as a lower homolog of one having the structure VIII but with the side chain in the furan ring, has been prepared by Karrer and Widmer.[7] It is a solid melting at 103° and in alcohol solution gives a brown-red color with ferric chloride which changes to blue on the addition of water. It polymerizes readily on the addition of dilute sulfuric acid. Rotenol is quite stable to dilute sulfuric acid and melts at 60°.

On reduction with sodium and alcohol 2-methyl-5-hydroxycoumarone gives 2-methyl-5-hydroxycoumarane, which is a lower homolog of a substance having the structural formula VI, the proposed structure of dihydro "rotenol." 2-Methyl-5-hydroxycoumarane is a solid melting at 96° and in alcohol solution produces only a slight change with ferric chloride, which on the addition of water changes to a pale yellow. "Rotenol" has not yet been reduced to dihydrorotenol, which should correspond to the isopropyl homolog of 2-methyl-5-hydroxycoumarane. If, as Butenandt and Hildebrandt seem to believe, dihydrotubaic and dihydrorotenic acids are identical, then it must follow that dihydrotubanol and dihydrorotenol are also identical. Dihydrotubanol prepared by Takei has a melting point of 59° and does not give a color with ferric chloride.

Rotenic acid is fairly stable on fusion with potassium hydroxide. Bergapten[8] and xanthotoxin[9] also contain the furan ring, but in these it is opened on fusion with alkali.

It has been generally assumed that the carboxylic acid group in tubaic acid arises from the ketone group present in rotenone and the hydroxyl

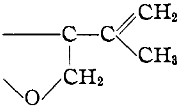
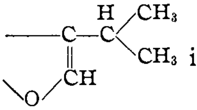
[7] P. Karrer and Fr. Widmer, *Helv. Chim. Acta*, **2**, 454 (1919).

[8] C. Pomeranz, *Monatsh.*, **12**, 379 (1891); **14**, 29 (1893).

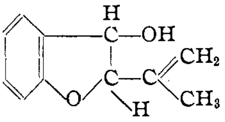
[9] H. Thoms, *Ber.*, **44**, 3325 (1911); **45**, 3705 (1912).

group is the result of the opening of the lactone ring. The lactone ring in rotenone is readily opened on catalytic hydrogenation to give an acid, whereas isorotenone in which the lactone ring is still present does not give an acid on catalytic hydrogenation. Furthermore, the double bond in rotenone which is readily reduced has disappeared in isorotenone. In the formula proposed by Takei and by Butenandt and Hildebrandt one would not expect any difference in behavior of the lactone ring on catalytic hydrogenation of rotenone and isorotenone.

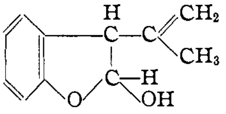
It seems reasonable to assume that the shifting of the double bond is responsible for the difference in behavior of the two lactones but if the OH group is assumed to be attached to the benzene ring as it is in the formulas of Takei and of Butenandt and Hildebrandt, this difference would not be expected.

If as stated above the other half of the rotenone molecule was joined through the hydroxyl group and the carbonyl group, it would give a substance having in its molecule a  group in rotenone and a  in isorotenone. Both types of groupings are very sensitive to sulfuric acid, giving rise to polymerization products. Rotenone is converted to isorotenone with sulfuric acid and isorotenone is very stable to sulfuric acid.

Also the fact that tubanol does not give a color with ferric chloride, and its stability toward sulfuric acid, lead us to believe that the structural formula IX or X more nearly represents all the known reactions of tubanol.



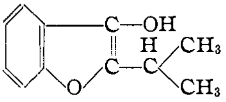
IX



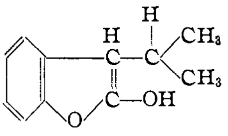
X

A substance having one of these two structures would not be expected to give a color test with ferric chloride, would be optically active and would be expected to be fairly stable toward sulfuric acid.

The structural formula XI or XII is proposed for "rotenol."



XI

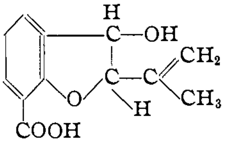


XII

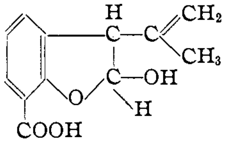
The questionable hydroxamic acid which Takei[10] obtained from rotenic acid methyl ether and hydroxylamine hydrochloride may be the oxime obtained by saponification of the methoxyl group and subsequent reaction with hydroxyl amine. Substances of the type XI react with hydroxylamine to give oximes.[11]

"Rotenol" gives a violet-red color with ferric chloride, which would be expected of a substance having the structure XI or XII.

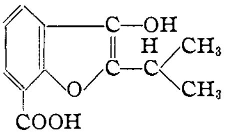
The structural formula XIII or XIV is proposed for tubaic acid, and XV or XVI is suggested for rotenic acid. These structures satisfactorily account for all the known facts. They would be expected to lose carbon dioxide readily on heating and their chemical behavior would be similar to that of tubanol and "rotenol." Attempts to synthesize some of these compounds are now under way.



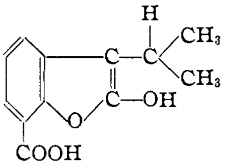
XIII



XIV



XV



XVI

In the course of our experimental work we have succeeded in simplifying the preparation of tubaic and rotenic acids and in improving the yields.

Experimental

Tubaic Acid.[12]—Ten grams of rotenone was added to a solution of 5 g. of potassium hydroxide in 100 cc. of 95% alcohol. The solution was refluxed in a boiling water-bath for three hours and then poured into 500 cc. of water. Carbon dioxide was passed into the turbid solution until precipitation was completed. The solution was filtered and allowed to stand at room temperature overnight. By morning usually another amorphous product had settled out. This was filtered off and the filtrate was acidified to congo red with 20% sulfuric acid. The resulting precipitate was filtered off and dissolved in ether. The filtrate was extracted three times with ether and the combined ether extracts were washed with water and then dried over anhydrous sodium sulfate. The ether was removed and the remaining tubaic acid was recrystallized from ether–petroleum ether. The yield was 1.5 g. Tubaic acid melts at 129° and when heated to 185–200° gives off carbon dioxide. In alcohol solution it gives a violet color with ferric chloride.

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[10] S. Takei, *Ber.*, **61**, 1003 (1928).

[11] K. v. Auwers and W. Müller, *ibid.*, **50**, 1149 (1917).

[12] S. Takei (a) *Biochem. Z.*, **157**, 1 (1925); (b) S. Takei and M. Koide, *Ber.*, **62**, 3030 (1929).

Tubanol.—The procedure for the preparation of this compound was the same as that described by Takei.[12b] It is a thick viscous liquid: n_D^{20} 1.5623.

Rotenic Acid.—Rotenic acid was prepared from isorotenone by the same procedure employed in the preparation of tubaic acid. It melted at 186° with decomposition. In alcohol solution it gives an intensely blue color with ferric chloride.

Summary

An improved procedure for the preparation of tubaic and rotenic acids is given. Structural formulas are proposed for tubanol, "rotenol" and tubaic and rotenic acids.

WASHINGTON, D. C.

[A COMMUNCATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

THE ALCOHOLYSIS OF CERTAIN 1,3-DIKETONES IN THE PRESENCE OF HYDROGEN CHLORIDE

BY HOMER ADKINS, WALTER KUTZ AND DONALD D. COFFMAN

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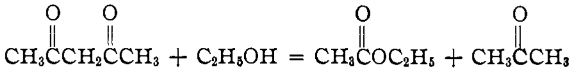
In the course of a study of the relationship of the constitution of the reactants to the point of equilibrium attained in the Claisen or acetoacetic ester condensation it seemed advisable to determine the rate of alcoholysis of a number of 1,3-diketones in the presence of hydrogen chloride. A typical reaction is as follows



$$CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}CH_3 + C_2H_5OH = CH_3\overset{\overset{O}{\|}}{C}OC_2H_5 + CH_3\overset{\overset{O}{\|}}{C}CH_3 \qquad (1)$$

The alcoholysis of the diketones and analysis of the resultant solution for ethyl acetate were carried out as follows. Approximately 1×10^{-2} mole of the diketone was dissolved in dry ethanol, and a normal alcoholic solution of hydrogen chloride added so that the volume of the reaction mixture was 40 ml. and the desired amount of catalyst was present. If the amount of ethyl acetate expected in a reaction mixture was less than about 2×10^{-3} moles, the amounts of the reactants were increased so that at least that much ester would be present in the solution to be analyzed.

The reaction mixture contained in a 50-ml. tightly stoppered flask was placed in a thermostat and held at 60° for the desired length of time. The reaction was stopped by adding 2 ml. of phenylhydrazine. The mixture was then thoroughly shaken and cooled. The reaction flask, which bore on its side a Vigreux fractionating column 15 cm. in length, was then placed in an oil-bath whose temperature was slowly raised to 120° during the course of an hour or until the flask was dry. Three successive 10-ml. portions of dry ethanol were added to the residue in the flask and distilled out. The total time for the distillation was from two to three hours. An