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

ROTENONE.
IX. ALKALI FUSION OF SOME DERIVATIVES OF ROTENONE

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The rotenone molecule is generally assumed to consist of two component parts joined by a chain of carbon atoms containing the carbonyl group. On treatment with alcoholic potassium hydroxide, tubaic acid, a monohydroxy monocarboxylic acid of formula $C_{12}H_{12}O_4$ is obtained, which is converted into isotubaic acid[1] (rotenic acid) by fusion with potassium hydroxide or by treatment with sulfuric acid. Isotubaic acid is obtained directly by alkali fusion of rotenone or from isorotenone either by fusion or by treatment with alcoholic potassium hydroxide. Butenandt[1] has assumed that the rotenone molecule is cleaved at the carbonyl group either by hydrolysis or oxidation, because dihydrodesoxyrotenone, in which the carbonyl group is not present, is stable toward alkalies.

Tubaic and isotubaic acids are very closely related, differing from each other in the position of the reducible double bond. The characteristic nucleus of tubaic acid is assumed to be present in the rotenone molecule.

Of the four oxygen atoms of tubaic acid, two are contained in the carboxyl group, one is present as a hydroxyl group and the fourth cannot be brought into reaction and therefore is assumed to be in the form of an ether linkage, in which form it is also supposed to be present in rotenone itself.

In a previous article[2] we reported that isotubaic acid is formed from derritol under the same conditions as from rotenone. This fact seems remarkable since all six of the oxygen atoms in derritol can be characterized with certainty, as it had been shown that derritol contains no indifferent oxygen but a phenolic group in addition to the original carbonyl, lactone and two methoxyl groups of rotenone.[3] The acid which Butenandt obtained in minute quantity by boiling derritol in strong alcoholic potassium hydroxide solution may have been tubaic acid.[1] In the process of fusion the tubaic acid which is first formed is isomerized into isotubaic acid.

Since all the oxygen atoms in derritol are accounted for, it must follow that the indifferent oxygen in isotubaic acid is formed in the process of

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[1] In this article we have used the word isotubaic acid instead of rotenic acid for the reason that the hydroxyl derivative obtained by elimination of the carboxyl group was named rotenol by Takei after this word had been used by Butenandt, *Ann.*, **464**, 253 (1928), to designate the zinc alkali reduction product of rotenone. This older name should be retained and the more logical isotubaic acid and isotubanol substituted for the terms rotenic acid and rotenol.

[2] H. L. Haller and F. B. LaForge, THIS JOURNAL, **52**, 2480 (1930).

[3] (a) A. Butenandt, *Ann.*, **464**, 253 (1928); (b) F. B. LaForge and L. E. Smith, THIS JOURNAL, **52**, 1088 (1930).

fusion and that the characteristic grouping of tubaic acid is not part of the derritol molecule, but must be regarded as a secondary decomposition product. Whether or not the nucleus of tubaic acid is actually part of the rotenone molecule is therefore open to doubt, even though the isomerization of rotenone to isorotenone and of tubaic to isotubaic acid may be due to the shifting of a double bond in the side chain, as is now generally accepted.

These considerations led us to subject a number of characteristic rotenone derivatives to the alkali fusion process in order to determine which of them yielded acids of the tubaic acid type.

The method employed was in all cases essentially the same as that described for the preparation of isotubaic acid from rotenone.[2,4]

Both derritol and isoderritol[5] yielded isotubaic acid but the yield was less in the case of isoderritol. Dehydrorotenone[1] also gave isotubaic acid. Dihydroxyrotenonic acid, $C_{23}H_{24}O_8$ (Derris säure, Butenandt) and its isomer, isodihydroxyrotenonic acid, which on oxidation with hydrogen peroxide in alkaline solution yield derric acid,[6] also gave isotubaic acid on alkali fusion.

Rotenol (Butenandt),[1] which is supposed to contain no carbonyl group but a secondary alcoholic group in its place, contrary to our expectation, gave a yield of isotubaic acid three times greater than that obtained from rotenone.

It has been generally assumed that the carboxyl group in tubaic and isotubaic acids arises from the ketone group in rotenone which joins the two halves of the molecule, one of which corresponds to tubaic acid and the other to derric acid. The fact that isotubaic acid is easily obtained from rotenol on fusion with alkali contradicts this assumption. The possibility that the hydroxyl group is oxidized to the ketone group during the fusion process still remains, but the smooth manner in which the fusion proceeds, the slight amount of charring which takes place, and the greater yield of isotubaic acid incline us to doubt that this has happened.

On fusion of dihydroderritol methyl ether,[3b] a small quantity of a methoxyl-free phenolic acid was obtained which melted at 186° and gave the same color reaction with ferric chloride as did isotubaic acid. However, when this acid was mixed with isotubaic acid the melting point was twenty degrees lower than the melting point of isotubaic acid, and it could be sharply distinguished from isotubaic acid by an optical examination of the crystals, as well as by its different solubility in 40% alcohol. In another attempt to obtain a larger quantity of this acid, five grams of dihydroderritol methyl ether was fused with alkali under slightly different conditions, but in this case dihydrotubaic acid was obtained.

[4] S. Takei, *Biochem. Z.*, 157, 1 (1925).

[5] F. B. LaForge and L. E. Smith, THIS JOURNAL, 51, 2574 (1929).

[6] F. B. LaForge and L. E. Smith, *ibid.*, 52, 1091 (1930).

All the derivatives mentioned above contain either the original lactone group of rotenone, or, as in the case of the two dihydroxyrotenonic acids, the hydrolyzed lactone group.

The lactone group of rotenone and most of its derivatives may also be opened by catalytic hydrogenation, with the formation of acids.[5] By this process rotenonic acid, $C_{23}H_{24}O_6$, is obtained from rotenone and corresponding acids are obtained by this reaction from dehydrorotenone, rotenol and derritol methyl ether.[3b] Except in the case of rotenone, the double bond originally present is also reduced by this process, and the dihydro acids are obtained. Several acids of this type were fused with potassium hydroxide in the usual manner, but in no case could isotubaic or dihydrotubaic acid be obtained. In most of the experiments only a very small quantity of a crystalline product could be isolated from the reaction mass, and in the case of rotenonic acid, the acid obtained could not be crystallized.

In the case of dehydrodihydrorotenonic acid[6] and dihydrorotenolic acid[3b] a small quantity of a phenolic acid was obtained, but it was definitely established by crystallographic methods that it was neither isotubaic acid nor dihydrotubaic acid.

Such of the above-mentioned compounds as gave isotubaic or dihydrotubaic acids contain the lactone group, or this group has been opened by hydrolysis, and it may be concluded that the hydroxyl group resulting from the opening of the lactone ring is necessary for the formation of isotubaic or dihydrotubaic acid.

The fact that isotubaic acid is obtained from rotenol (Butenandt) contradicts the theory that cleavage takes place at the carbonyl group, and the results as a whole indicate that tubaic acid may be a secondary cleavage product of rotenone.

Experimental

Alkali Fusion of Derritol.—Two grams of derritol was intimately mixed with 2 g. of finely powdered potassium hydroxide in a nickel crucible, and 1 cc. of water was added. Eighteen grams of powdered potassium hydroxide was then added, and the mixture heated in a metal-bath. The reaction mass was held at 205–210° for one hour with constant stirring. The temperature of the metal-bath was 250–270°. The melt was then slowly poured onto cracked ice and the resulting dark reddish-brown solution was saturated with carbon dioxide. The solution, after being filtered to remove a small quantity of tarry matter which sometimes separated, was acidified with dilute sulfuric acid and extracted four times with ether. The combined ether extracts were dried over sodium sulfate and the ether was removed. The remaining tarry residue was extracted with boiling petroleum ether (b. p. 57–70°). On concentrating this extract, isotubaic acid was obtained. The yield was 0.2 g. It was recrystallized from 40% alcohol. It melted at 184° and its optical properties[7] were identical with those of isotubaic acid. A mixture of this substance and isotubaic acid obtained from isorotenone had a melting point of 183°.

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[7] We are indebted to Mr. George L. Keenan of the Food and Drug Administration for the determination of the optical properties.

The conditions described for the alkali fusion of derritol were duplicated as closely as possible in the fusion of the other compounds.

Alkali Fusion of Rotenol.—Two grams of rotenol on fusion at 200–210° for one-half hour yielded 0.65 g. of substance. After recrystallizing from 40% alcohol, it melted at 184°, and its optical properties were identical with isotubaic acid. When it was mixed with authentic isotubaic acid, the melting point was 184°.

Alkali Fusion of Isoderritol.—Two grams of isoderritol was fused in the manner described for derritol except that the water was omitted. The fusion temperature was 205°, which was maintained for one-half hour. The yield of substance from petroleum ether was about 0.1 g. After recrystallizing from 40% alcohol, it melted at 182°, and its optical properties could not be differentiated from those of isotubaic acid. When it was mixed with isotubaic acid, the melting point was 182°.

Alkali Fusion of Dihydroderritol Methyl Ether.—Two grams of dihydroderritol methyl ether was fused in the usual manner at 205° for one-half hour. The acid obtained from petroleum ether was recrystallized from 25% alcohol. It melted at about 174° and lost carbon dioxide at 180°. The melting point varied with the rate of heating. It was methoxyl free. In alcohol solution it gave a blue color with ferric chloride which could not be differentiated from the color given by isotubaic acid under the same conditions. However, its optical properties did not agree with those of isotubaic acid, and when it was mixed with isotubaic acid the melting point was 160°.

Anal. Subs., 0.0214: required 1.08 cc. $N/10$ alkali; 0.0204 g. subs. required 1.01 $N/10$ alkali; acid number calcd., 198, 201.

In an attempt to prepare a larger quantity of this acid, 5 g. of dihydroderritol methyl ether was fused, but dihydrotubaic acid was obtained. The acid melted at 168° and a mixture of this acid and dihydrotubaic acid had a melting point of 168°.

Alkali Fusion of Dihydroxyrotenonic Acid.—Two grams of acid was fused at 205° for one-half hour in the usual manner except that the water was omitted. The acid obtained melted at 184° and was identified as isotubaic acid by its optical properties and its melting point when mixed with isotubaic acid.

Alkali Fusion of Isodihydroxyrotenonic Acid.—This substance when fused in the usual manner yielded isotubaic acid, which was identified in the manner described above.

Alkali Fusion of Dehydrorotenone.—Two and one-half grams of dehydrorotenone on fusion in the usual manner at 205° for one-half hour yielded isotubaic acid, which was identified as described above.

Alkali Fusion of Rotenonic Acid.—Two grams of rotenonic acid was fused in the manner described above with and without the addition of water, but in no instance was it possible to obtain a crystalline derivative. Dihydrorotenonic acid behaved similarly.

Alkali Fusion of Dehydrodihydrorotenonic Acid.—Two grams of dehydrodihydrorotenonic acid on fusion in the usual manner yielded a small quantity of acid, which was recrystallized from dilute alcohol. It melted somewhat indefinitely at 175°. Its crystallographic properties were totally different from those of dihydrotubaic acid.

Alkali Fusion of Dihydrorotenolic Acid.—Two grams of dihydrorotenolic acid was fused in the usual manner at 205° for half an hour. On recrystallization from dilute alcohol a very small quantity of acid was obtained which melted at 159° but not sharply. When mixed with dihydrotubaic acid the melting point was 135–140°, with previous softening at 125°. The optical properties of the compound were found to be different from those of dihydrotubaic acid.

Summary

Several derivatives of rotenone have been submitted to the alkali fusion process.

Derritol, isoderritol, rotenol, dihydroxyrotenonic acid and isodihydroxyrotenonic acid on alkali fusion yielded isotubaic acid.

Rotenonic acid, as well as several other derivatives of rotenone in which the lactone group was opened by catalytic reduction, did not give isotubaic or dihydrotubaic acid on fusion with alkali.

Compounds which gave isotubaic or dihydrotubaic acid contain the lactone group or this group has been opened by hydrolysis. The conclusion is drawn that the hydroxyl group resulting from the opening of the lactone ring is necessary for the formation of isotubaic or dihydrotubaic acid.

The fact that rotenol gives isotubaic acid contradicts the theory that cleavage of the molecule takes place at the ketone group.

The nucleus of tubaic acid does not exist in derritol as such, but is a secondary decomposition product. Perhaps it does not exist in rotenone.

Substance	Product of alkali fusion
Derritol	Isotubaic acid
Isoderritol	Isotubaic acid
Rotenol	Isotubaic acid
Dihydroxyrotenonic acid	Isotubaic acid
Isodihydroxyrotenonic acid	Isotubaic acid
Dehydrorotenone	Isotubaic acid
Dihydroderritol methyl ether	Dihydrotubaic acid
Rotenonic acid	....
Dehydrodihydrorotenonic acid	Unidentified phenolic acid
Dihydrorotenolic acid	Unidentified phenolic acid

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THE COMPOSITION OF SALKOWSKI'S ARABAN

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Introduction

Most of the methods devised in the attempt to prepare pure xylans have involved the use of alkaline copper solutions in the process of purification.[1]

It was shown by Salkowski that no precipitate was formed when Fehling's reagent was added to a solution of gum arabic, but that on further addition of sodium hydroxide a precipitation was brought about. The substance precipitated was hydrolyzed with 2% sulfuric acid and formed large amounts of arabinose. On oxidation of the hydrolysate with nitric acid, there was no evidence of the formation of mucic acid. Because of these facts, Salkowski called the substance an araban.

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[1] Salkowski, *Z. physiol. Chem.*, **34**, 162 (1901); **35**, 240 (1902); **117**, 48 (1921); Henser and Braden, *J. prakt. Chem.*, **103**, 69 (1921); **104**, 259 (1922); Link, THIS JOURNAL, **51**, 2506 (1929); **52**, 2091 (1930).