

hydrolysis. These statements hold, also, when both radicals contain the sulfonyl group.

3. The results of the present study indicate that the repulsion energy of atomic kernels cannot be the sole factor in the migration of acyl radicals between nitrogen and oxygen in an ortho aminophenol derivative.

4. Attempts to prepare diacyl derivatives from 2-amino-4,6-dinitrophenol were unsuccessful.

5. Further work is in progress.

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

ROTENONE. XIV. THE RELATION OF THE OPTICAL ACTIVITY OF SOME ROTENONE DERIVATIVES TO THE STRUCTURE OF TUBAIC ACID

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RECEIVED JUNE 8, 1931

PUBLISHED SEPTEMBER 5, 1931

In the early stages of the investigations on the structure of rotenone, it was found that the compound is decomposed by alcoholic potassium hydroxide, yielding tubaic acid¹ (C₁₂H₁₂O₄) in variable but small quantities. Considerable work has been done on this decomposition product, especially by the Japanese investigators, and it seems fairly well established that tubaic acid contains an indifferent (ether) oxygen atom as well as an hydroxyl group, in addition to the carboxyl group and an isoallyl side chain which can be reduced to the isopropyl group. The isomerization of tubaic acid is due to the shifting of a double bond,² forming the isopropyl group. This change is apparently the same as that which takes place when rotenone is isomerized to isorotenone.

Except for this one reaction, tubaic and isotubaic acids show none of the typical reactions of rotenone or isorotenone, and the question as to whether the nucleus of tubaic acid is actually present in rotenone, as is assumed by Takei and his co-workers³ is one of considerable importance.

For a number of reasons we are inclined to reject this assumption. The first and most important reason for our objection is the fact that derritol, which beyond any doubt has the formula C₂₁H₂₂O₆, yields tubaic and isotubaic acid, as does rotenone and many other of its derivatives. In derritol all six of the oxygen atoms have been definitely characterized.

¹ T. Kariyone, V. Kimura and K. Kondo, *J. Pharm. Soc. (Japan)* No. 514, 1094 (1924); *ibid.*, No. 518; 377 (1925); S. Takei, *Ber.*, **61**, 1003 (1928).

² A. Butenandt and F. Hildebrandt, *Ann.*, **477**, 245 (1930); S. Takei, M. Koide and S. Miyajima, *Ber.*, **63**, 1369 (1930).

³ S. Takei, S. Miyajima and M. Ono, *ibid.*, **64**, 1000 (1931).

They are contained in the two methoxy groups, the carbonyl group, the phenolic hydroxyl⁴ and the lactone groups. That the lactone group is present is shown by the fact that methyl derritol is easily converted into an acid by hydrogenation. The phenolic group, moreover, is attached to the same benzene nucleus which already bears the two methoxy groups, and it can only be assumed that it arises by the opening of the ether linkage. It follows, therefore, that the indifferent oxygen in tubaic acid is not the same as the indifferent oxygen in rotenone. It also has been shown⁵ that the hydroxyl group formed on hydrolytic opening of the lactone ring is necessary for the formation of tubaic acid. Repeated attempts to obtain a crystalline derivative on alkali fusion of rotenonic acid,⁶ which is easily obtained on catalytic hydrogenation of the lactone group of rotenone, resulted in failure.

In their latest paper Takei and his co-workers⁸ proposed a structure for rotenone and state that dihydrorotenonic acid should yield desoxydihydrotubaic acid. Many attempts have been made in this Laboratory to obtain this acid from dihydrorotenonic acid, but without success. It should be prepared more easily than dihydrorotubaic acid, if the formula proposed for rotenone is right, because coumarone derivatives are known to be very stable to alkali.

Repeated attempts to obtain a primary degradation product of rotenone containing the isopropylene group or a methoxy-free derivative have not yet met with success. However, a study of the rotatory power of derivatives of rotenone has given facts which permit some conclusions regarding the structure of tubaic acid.

Rotenone contains two asymmetric centers.⁷ One, in this paper called asymmetric center I, disappears when dehydro derivatives are prepared; the other, termed asymmetric center II, disappears when rotenone and its derivatives are isomerized to the iso series. Thus dehydrorotenone⁸ is optically active, but dehydroisorotenone is optically inactive.

As another item of considerable importance, it has now been found that an asymmetric center disappears on catalytic hydrogenation of the lactone group to a desoxy acid, but when the lactone group is opened by hydrolysis, as in the formation of derrissic acid⁸ (derrissäure), optical activity is retained. For example, it has been found that dehydrodihydrotentenonic acid⁹ is optically inactive, whereas derrissic acid is optically active. Isoderrissic acid, however, is optically inactive. As derrissic acid is formed from dehydrorotenone, it owes its optical activity to asymmetric center II.

⁴ L. E. Smith and F. B. LaForge, *THIS JOURNAL*, **52**, 4595 (1930).

⁵ H. L. Haller and F. B. LaForge, *ibid.*, **52**, 4505 (1930).

⁶ F. B. LaForge and L. E. Smith, *ibid.*, **51**, 2574 (1929).

⁷ A. Butenandt and F. Hildebrandt, *Ann.*, **477**, 245 (1930).

⁸ A. Butenandt, *ibid.*, **464**, 254 (1928).

⁹ F. B. LaForge and L. E. Smith, *THIS JOURNAL*, **52**, 1091 (1930).

In this acid the lactone group has been opened by hydrolysis, yielding an hydroxy acid, whereas in dehydrodihydrorotenonic acid the lactone has been opened by hydrogenation, forming a desoxy acid.

The conclusion that may be drawn from the data given above is that the oxygen bridge of the lactone group is attached to an asymmetric carbon atom containing one hydrogen atom. When the lactone group is opened by hydrogenation, the asymmetric carbon atom acquires another hydrogen atom and loses its asymmetry, whereas when the lactone is opened by hydrolysis the asymmetric center is retained.

Rotenol,⁸ derritol methyl ether,¹⁰ and dehydrorotenol¹¹ are optically active, but the desoxy acids derived from them by catalytic hydrogenation are optically inactive.

A further reason for an objection to the primary nature of tubaic acid is that rotenol yields netoric acid⁴ of formula $C_{12}H_{14}O_5$, which contains the methoxyl groups together with an indifferent oxygen atom, and that rotenol gives tubaic acid even more readily than does rotenone.

As the lactone group is necessary for the formation of tubaic acid it follows that any structure proposed for this substance must have an oxygen atom attached to an asymmetric carbon atom. The view¹² has been expressed that the formula proposed by Takei for tubaic acid is incorrect, and the foregoing offers additional proof. Attempts in this Laboratory to synthesize a compound having the formula proposed by Takei so far have resulted in failure, but attempts to prepare compounds possessing the formula proposed by us have also been unsuccessful.

In the course of the experiments it has been found that when rotenonic acid is refluxed in alcoholic potash in the same way that rotenone is treated for the preparation of tubaic acid, the acid is not cleaved. Instead, an acid is obtained which has the same empirical formula as rotenonic acid, but it melts at 184° whereas rotenonic acid melts at 206° . That the change which has taken place is simply one of optical inactivation of the rotenonic acid was demonstrated in the following manner:

When rotenonic acid is dissolved in sulfuric and acetic acids an optically active lactone (β -dihydrorotenone (I) m. p. 156°)¹³ is obtained. On oxidation with alkaline ferricyanide, β -dihydrorotenone yields dehydro- β -dihydrorotenone,¹³ which is optically inactive. When dissolved in acid, rotenonic acid which has been inactivated by refluxing with alcoholic potash gives an inactive lactone (II) which melts at 171° . This lactone on oxidation with alkaline ferricyanide yields a product which is identical with dehydro- β -dihydrorotenone. Thus the two acids and the two lactones I

¹⁰ F. B. LaForge and L. E. Smith, *THIS JOURNAL*, **52**, 1088 (1930).

¹¹ H. L. Haller and F. B. LaForge, *ibid.*, **53**, 2271 (1931).

¹² H. L. Haller and F. B. LaForge, *ibid.*, **52**, 3207 (1930).

¹³ H. L. Haller, *ibid.*, **53**, 733 (1931).

and II are identical chemically, the difference in their physical properties being due to optical activity.

When dihydrorotenonic acid is refluxed with alcoholic potash, it is also inactivated and, like the optically active dihydrorotenonic acid, the resulting compound is not isomerized by sulfuric acid.

Butenandt has found that on prolonged reduction of rotenone, dihydrodesoxyrotenone is formed. This compound is more readily obtained from dihydrorotenone with amalgamated zinc. When rotenone and isorotenone are treated with this reagent, identical compounds are obtained, desoxyisorotenone ($C_{23}H_{24}O_5$). We have confirmed Butenandt's observations on the stability of dihydrodesoxyrotenone, and we have also found that desoxyisorotenone behaves similarly.

Experimental

***dl*-Rotenonic Acid.**—A solution of 10 g. of rotenonic acid ($[\alpha]_D^{20} +45^\circ$ in chloroform; *C*, 6.95) in 100 cc. of alcohol, 5 cc. of water and 5 g. of potassium hydroxide was refluxed for three hours. The cherry-red solution was poured into 800 cc. of water, and the solution was saturated with carbon dioxide. The precipitate was filtered off, washed with water and dissolved in ether. The ether extract was washed several times with water and then dried over sodium sulfate. When the ether was removed the substance readily crystallized. The yield was 8 g. It was recrystallized twice from 50% alcohol. It melted at 184° . It can also be recrystallized from methyl alcohol.

Anal. Subs., 0.0795: CO_2 , 0.2022; H_2O , 0.0438. Calcd. for $C_{23}H_{24}O_6$: *C*, 69.69; *H*, 6.06. Found: *C*, 69.40; *H*, 6.17.

***dl*-Dihydrorotenonic Acid.**—Dihydrorotenonic acid was freed from a small amount of rotenonic acid, which it almost always contains, by isomerizing the rotenonic acid to β -dihydrorotenone and separating the two by means of alkali. The dihydrorotenonic acid was crystallized from 50% alcohol. It melted at 216° . It can also be recrystallized from butyl ether or from methyl alcohol. In chloroform $[\alpha]_D^{20} +87^\circ$; *C*, 7.8. The purified dihydrorotenonic acid was refluxed with alcoholic potash and then worked up in the same way as described for rotenonic acid. Recrystallized several times from 50% alcohol it melted at 194° .

Reduction of *dl*-Rotenonic Acid to *dl*-Dihydrorotenonic Acid.—Two grams of *dl*-rotenonic acid was reduced in ethyl acetate solution with platinum oxide catalyst in the usual manner. The acid was recrystallized several times from 50% alcohol. It melted at 194° . It was found to be identical with the acid obtained on boiling dihydro-rotenonic acid with alcoholic potash. It can also be recrystallized from methyl alcohol.

Oxidation of *dl*-Rotenonic Acid with Hydrogen Peroxide.—Two grams of *dl*-rotenonic acid was dissolved in 25 cc. of 5% potassium hydroxide, and the solution was warmed to about 60° ; 3 cc. of 40% hydrogen peroxide was dropped in with constant stirring. Finally the solution was heated to boiling, then cooled and saturated with carbon dioxide. The precipitate was filtered off, dissolved in ether, washed with water and dried over sodium sulfate. The ether was removed, and the substance was crystallized from 50% alcohol. It melted at 133° . It is identical with the hydroxy-rotenonic acid obtained on oxidation of rotenonic acid with hydrogen peroxide.¹⁴

Anal. Subs., 0.0895; CO_2 , 0.2189; H_2O , 0.0469. Calcd. for $C_{23}H_{24}O_7$: *C*, 67.0; *H*, 5.83. Found: *C*, 66.71; *H*, 5.87.

¹⁴ F. B. LaForge and L. E. Smith, *THIS JOURNAL*, **52**, 3603 (1930).

dl- β -Dihydrorotenone.—The procedure described for isomerizing optically active rotenonic acid was employed for the isomerization of the racemized rotenonic acid. The lactone was recrystallized from methyl alcohol. It melted at 171°. In one instance a product was obtained which melted at 176° with previous softening at 171°.

Anal. Subs., 0.0824: CO₂, 0.2102; H₂O, 0.0449. Calcd. for C₂₃H₂₄O₆: C, 69.69; H, 6.06. Found: C, 69.57; H, 6.10.

Dehydro- β -dihydrorotenone from *dl*- β -Dihydrorotenone.—To 2 g. of *dl*- β -dihydrorotenone in 100 cc. of boiling alcohol was added 3.6 g. of potassium ferricyanide and 0.54 g. of potassium hydroxide in 30 cc. of water. The reaction mixture was allowed to stand overnight. About 600 cc. of water was then added, and the resulting precipitate was filtered off, washed with water and dried. It was recrystallized by dissolving it in boiling chloroform and adding four volumes of hot methyl alcohol. It melted at 269°. When mixed with an equal quantity of dehydro- β -dihydrorotenone no depression in melting point was observed. The substance was further identified as dehydro- β -dihydrorotenone by an examination of its optical properties.

Oxidation of *dl*- β -Dihydrorotenone with Iodine and Potassium Acetate.—When *dl*- β -dihydrorotenone was oxidized in alcohol solution with iodine and potassium acetate by the usual procedure β -dihydrorotenolone and its acetyl derivative were obtained.¹³

Desoxyisrotenone.—To 5 g. of isrotenone dissolved in 250 cc. of glacial acetic acid was added 30 g. of amalgamated zinc. Fifty cc. of concentrated hydrochloric acid was then added, and the reaction mixture was refluxed for two hours. The colorless solution was decanted from the zinc into 1 liter of water. The precipitate was filtered off, washed with water and then dissolved in ether. The ether extract was washed with 5% potassium hydroxide and then with water. The ether solution was dried over sodium sulfate. When most of the ether was removed, the substance crystallized. It was recrystallized from methyl alcohol and melted at 165–166°.

Anal. Subs., 0.0941; CO₂, 0.2495; H₂O, 0.0533. Calcd. for C₂₃H₂₄O₅: C, 72.63; H, 6.33. Found: C, 72.31; H, 6.30.

When rotenone was treated with amalgamated zinc in the manner described for isrotenone, a compound was obtained which melted at 165–166°. When this was mixed with an equal quantity of desoxyisrotenone, no depression in melting point was noted.

ROTATORY POWER OF ROTENONE DERIVATIVES^a

Substance	$[\alpha]_D^{20}$	<i>c</i>
Rotenol	-77.3	3.98
Dihydrorotenonic acid	0	6.07
Dehydrodihydrorotenol	-8.05	5.60
Dehydrodihydrorotenonic acid	0	5.36
Dihydroderritol methyl ether	-32.8	5.80
Methyl derritolic acid	0	4.97
Rotenonic acid	+45.0	6.95
Dihydrorotenonic acid	+67.0	7.77
Dehydrodihydrorotenonic acid	0	5.95
Desoxyisrotenone	-113.2	5.40
Isoderritol	0	5.30
Dihydrorotenone	-123.2	5.51
β -Dihydrorotenolone	0	2.5

^a Chloroform was used as the solvent for all substances except methyl derritolic acid and dehydrodihydrorotenonic acid, which were dissolved in a solution of 90% chloroform and 10% absolute alcohol.

Summary

The optical rotation of several rotenone derivatives has been determined. It has been found that one of the asymmetric centers in rotenone and its derivatives disappears when the lactone group is hydrogenated to a desoxy acid.

This observation together with a number of other known facts constitutes an argument against the presence in rotenone of the grouping characteristic of tubaic acid.

Rotenonic acid and dihydrorotenonic acid become optically inactive on treatment with alcoholic potash.

Rotenone and isorotenone are reduced with Clemmensen's reagent to isodesoxyrotenone.

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

DEGUELIN. III. THE ORIENTATION OF THE METHOXYL GROUPS IN DEGUELIN, TEPHROSIN AND ROTENONE

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RECEIVED JUNE 10, 1931

PUBLISHED SEPTEMBER 5, 1931

In a brief note recently published in *THIS JOURNAL*¹ it was reported that under certain conditions dehydrodeguelin was oxidized with potassium permanganate in such a manner that one of the main products of the reaction was an hydroxydimethoxybenzoic acid. The structure of this acid was established as that of one of three isomers, namely, 2-hydroxy-4,5-dimethoxy, 5-hydroxy-2,4-dimethoxy or 4-hydroxy-2,5-dimethoxybenzoic acid. The evidence upon which this was based was that upon methylation of the hydroxy acid, asaronic acid, 2,4,5-trimethoxybenzoic acid was obtained. The identity of asaronic acid was established by its melting point and also by the products obtained from it by bromination and nitration.

The hydroxy acid gave an intense blue color with ferric chloride, indicating that it was probably 2-hydroxy-4,5-dimethoxybenzoic acid. Attempts were made to synthesize this acid by diazotizing 2-amino-4,5-dimethoxybenzoic acid and replacing the diazonium group with hydroxyl. These experiments failed, however, so recourse was had to the procedure of decarboxylating the hydroxy acid by heating it with aniline and identifying the resulting dimethoxyphenol. This was accomplished without difficulty, and the properties of the phenol were established.

If the acid obtained from dehydrodeguelin is actually 2-hydroxy-4,5-dimethoxybenzoic acid, the phenol derived from it by decarboxylation would be 1-hydroxy-3,4-dimethoxybenzene. As this phenol has not been described, its synthesis was undertaken. The steps involved were the

¹ Clark, *THIS JOURNAL*, 53, 2007 (1931).