181. *Experiments on the Synthesis of Rotenone and its Derivatives. Part II. The Synthesis of Rissic Acid and of Derric Acid, and the Constitution of Rotenone, Deguelin, and Tephrosin.*

By ALEXANDER ROBERTSON.

ROTENONE, an active insecticidal principle which occurs in the root of *Derris elliptica*, was first isolated in the pure state by Nagai (*J. Tokyo Chem. Soc.*, 1902, **23**, 740), who showed that the compound was a ketone. Since then the substance has been the subject of extensive analytical investigations by several different groups of workers and a large number of degradation products have been described. Of these the most important appear to be dehydrorotenone, rotenol, derritol, and derrisic, derric, rissic, and tubaic acids. Despite the accumulated evidence the entire constitution of the rotenone molecule is not clear and the recent formulæ proposed for the compound by Takei, Miyajima, and Ono (*Ber.*, 1932, **65**, 279) and by LaForge and Haller (*J. Amer. Chem. Soc.*, 1932, **54**, 810) are fundamentally different. Moreover, the necessary arguments in each case are somewhat intricate and consequently the problem of the synthesis of rotenone and its degradation products appears to be of considerable interest.

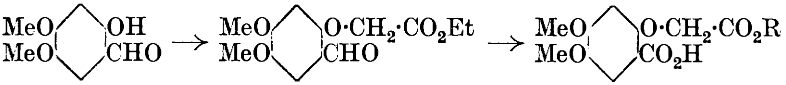
Rotenone, which is optically active (Ishikawa, *Tokyo Med. J.*, 1917, **31**, No. 4), was shown by Kariyone and his co-workers (*J. Pharm. Japan*, 1923, **491**, 10; 1924, **514**, 1049; 1925, **518**, 376) to contain a double bond and methoxyl groups and to give rise to tubaic acid, $C_{12}H_{12}O_4$, on fusion with potassium hydroxide. The accepted empirical formula, $C_{23}H_{22}O_6$, for the compound was first established by Takei (*Biochem. Z.*, 1925, **157**, 1) and confirmed by Butenandt (*Annalen*, 1928, **464**, 253). According to the observations of the latter author and of LaForge and his co-workers (*J. Amer. Chem. Soc.*, 1929, **51**, 2574; 1930, **52**, 1088, 1091, 3603) the rotenone molecule consists of two halves joined through a carbonyl group and may be written

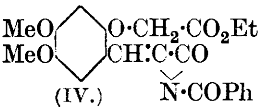
$$\underbrace{[C_9H_6O(OMe)_2]}_{\textit{Rissic acid}}\cdot CO\cdot\underbrace{[C_{11}H_{10}O_2]}_{\textit{Tubaic acid}}$$

Butenandt found that on treatment with zinc dust and alkali rotenone gave rise to rotenol, $C_{23}H_{24}O_6$, and derritol, $C_{21}H_{22}O_6$, whereas with mild oxidising agents the loss of two hydrogen atoms occurred with the formation of dehydrorotenone, $C_{23}H_{20}O_6$. On hydrolytic decomposition with aqueous alkali the last compound was converted into a monobasic acid, derrisic acid, $C_{23}H_{24}O_8$.

By the oxidation of derritol and of dehydrorotenone LaForge, Haller, and Smith (*J. Amer. Chem. Soc.*, 1931, **53**, 4400) obtained a hydroxydimethoxybenzoic acid identical with the acid isolated by Clark (*ibid.*, p. 3431) from dehydrodeguelin, a compound which is isomeric with rotenone and occurs along with it in *Derris elliptica*. This acid Clark believed to be 2-hydroxy-4 : 5-dimethoxybenzoic acid. On oxidation with alkaline hydrogen peroxide derrisic is degraded to derric acid, which is further oxidised by potassium permanganate to rissic acid (LaForge and Smith, *J. Amer. Chem. Soc.*, 1930, **52**, 1091, 2878; Takei and co-workers, *Ber.*, 1931, **64**, 1006). Since rissic acid on thermal decomposition was found to give 3 : 4-dimethoxyphenoxyacetic acid, LaForge (*J. Amer. Chem. Soc.*, 1931, **53**, 3896) adopted formula (III, R = H) for this compound and (VI) for derric acid (compare Takei, Miyajima, and Ono, *loc. cit.*).

In Part I * (J., 1931, 2432) the constitution of Clark's acid was established by synthesis. While the evidence for the constitution of rissic acid and of derric acid, though of an indirect nature, appeared to be substantial, it was realised that a β-phenoxypropionic acid structure for the latter substance was not excluded. In view of the important bearing which these acids have on the constitution of rotenone and of deguelin and tephrosin (Clark, *J. Amer. Chem. Soc.*, 1931, **53**, 729, 2372) it was resolved to place their structure beyond doubt by means of synthetical experiments.


(I.) (II.) (III.)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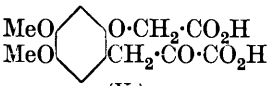
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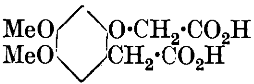
(VI.)

The preparation of the required intermediate (II) from the aldehyde (I) depends on the observation that esters of phenoxyacetic acids are readily formed by the interaction of ethyl bromoacetate and a phenolic compound in the presence of potassium carbonate in boiling acetone. By this method reactive groups, *e.g.*, CHO, CO_2Me, etc., already present in the phenolic nucleus are unaffected, and further, it permits the use of acyl groups as a means of protecting specific hydroxyl groups in the preparation of hydroxyphenoxyacetic acids. On oxidation, (II) gave rise to the *ester* (III, R = Et),

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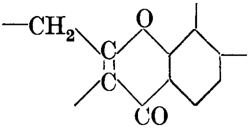
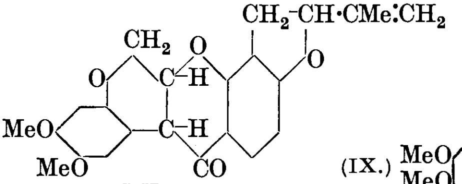
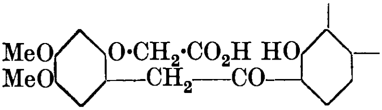
* This paper, which was in the nature of a preliminary note, is now regarded as Part I of this series of memoirs.

which on hydrolysis afforded 2-carboxy-4 : 5-dimethoxyphenoxyacetic acid (III, R = H) identical with rissic acid. This compound is most conveniently characterised by means of its methyl ester (Takei and co-workers, *Ber.*, 1931, **64**, 248). The conversion of (II) into derric acid (VI) proceeded smoothly by Mauthner's method (*Annalen*, 1909, **370**, 368) through the stages (IV) and (V). The formulæ (III, R = H) and (VI) proposed by LaForge (*loc. cit.*) for rissic acid and derric acid respectively are therefore confirmed and in consequence the structures recently proposed for rotenone and dehydrorotenone by Takei, Miyajima, and Ono (*loc. cit.*) are definitely excluded.

It was believed that the structure of rotenone might possibly be related to that of brazilin (Perkin and Robinson : for references, see Perkin and Everest, "Natural Organic Colouring Matters," 1918, pp. 345—383). Though a comparative survey of the chemistry of the two compounds indicated important differences in their constitutions, certain resemblances were noted (*e.g.*, the relationship of rissic acid to 2-carboxy-5-methoxyphenoxyacetic acid) and the author was led to adopt the new structures * for rotenone (VII) and dehydrorotenone (VIII) which have recently been suggested by La Forge and Haller (*loc. cit.*).


(VIII.)


(VII.)

(IX.) 

The reasons which led to this conclusion were practically identical with those set forth by Haller and LaForge and need not be discussed here. In further support of the structures (VII) and (VIII), however, it may be noted that (VII) contains a dihydro-1 : 4-pyrone nucleus and that the formation of the dehydro-compounds of the *iso*flavone type (VIII) (Baker and Robinson, J., 1925, **127**, 1981) offers an analogy with the transformation of a flavanone into a flavone. Similarly the hydrolysis of dehydrorotenone (VIII) to derrisic acid (IX) is directly analogous to the decomposition of an *iso*flavone.

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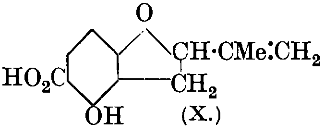
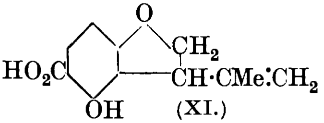
* The author's views on the constitution of rotenone and related substances were communicated privately to Professor R. Robinson, F.R.S., of Oxford University on January 20th, 1932, before the publication of the memoir by Haller and LaForge (*loc. cit.*) on February 5th, 1932.

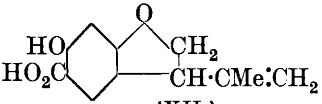
In this formula for rotenone (VII) the tubaic acid residue is represented as an integral part of the molecule and is formulated on the basis of the structure (X) proposed for tubaic acid by Haller and LaForge (*J. Amer. Chem. Soc.*, 1931, **53**, 4460). As far as the available direct experimental evidence goes, the latter compound may equally well have formula (XI) (Takei and co-workers, *Ber.*, 1931, **64**, 1000). In support of formula (X) or (XI) and in opposition to formula (XII) for tubaic acid it may be mentioned that the ferric chloride reactions of this acid and its derivatives closely resemble those of certain compounds of 2 : 6-dihydroxytoluene (*e.g.*, 2-hydroxy-4-methoxy-3-methylbenzoic acid) recently prepared in this laboratory.



(X.)



(XI.)



(XII.)

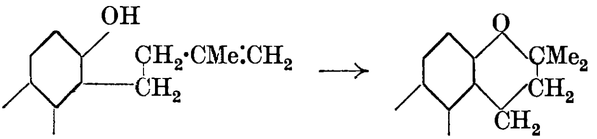
The opening of the dihydrofuran ring in certain derivatives of rotenone by catalytic hydrogenation is accompanied by the destruction of the optically active centre which is situated in the tubaic acid residue. This fact lends support to the view that the *iso*allyl group is in the 2-position of the dihydrofuran ring (X), since racemisation in this manner would be less likely to occur in a structure of the type (XI).

The Constitution of Deguelin and Tephrosin.

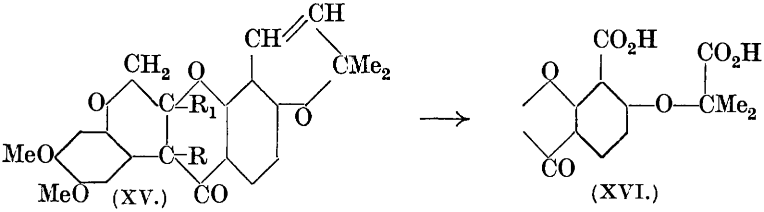
It has been established by Clark (*loc. cit.*) that in addition to rotenone there occur in *Derris elliptica* two closely related substances, tephrosin (Hanriot, *Compt. rend.*, 1907, **144**, 150) and deguelin. The latter compound, which is optically inactive, is an isomeride of rotenone and appears to contain the same dihydro-1 : 4-pyrone nucleus. Dehydrodeguelin, which is formed in the same manner as and is isomeric with dehydrorotenone, on treatment with alkali gives rise to deguelic acid, an isomeride of derrisic acid. The structure of deguelic acid must be closely related to that of derrisic acid, since on oxidation it yields derric acid (VI) and rissic acid (III) (Clark, *J. Amer. Chem. Soc.*, 1931, **53**, 2369). Inspection of the formula of derrisic acid (IX) indicates that the structural difference between it and deguelic acid must lie in the tubaic acid residue.

It is now accepted that the so-called deoxy-acids formed by the catalytic hydrogenation of rotenone and certain of its derivatives are in reality phenols and arise by the opening of the dihydrofuran ring. Thus the phenol rotenonic acid (Butenandt, *loc. cit.*) may be represented by a formula of the type (XIII).

(XIII.)



(XIV.)



(XV.) (XVI.)

This substance on treatment with a mixture of acetic and sulphuric acids gives rise to β-dihydrorotenone, which has no longer the properties of a phenol. It retains the dihydro-1 : 4-pyrone nucleus of rotenone, since on oxidation it yields dehydro-β-dihydrorotenone, which on treatment with alkali is converted into dehydrodihydroxy-β-dihydrorotenonic acid (Haller, *J. Amer. Chem. Soc.*, 1931, **53**, 733). The latter compound, which may be more conveniently named β-dihydroderrisic acid, is a true monobasic, phenolic acid and on oxidation with alkaline hydrogen peroxide yields derric acid (VI). The β-series of rotenone derivatives, therefore, is produced by a rearrangement of the elements of the dihydrofuran residue in compounds of the type (XIII), and hence it appears justifiable to conclude that this rearrangement results in the formation of a chroman ring (type XIV).

On catalytic reduction dehydrodeguelin gives rise to a dihydro-derivative identical with dehydro-β-dihydrorotenone. Similarly dihydrodehydrodeguelic acid is identical with β-dihydroderrisic acid (Clark, *loc. cit.*). Therefore dihydrodeguelin and its derivatives may be represented by formulæ of the type (XIV). As a result of the close resemblance between dehydrorotenone and dehydrodeguelin (type VIII) it is reasonable to assume that in the latter compound the catalytically reducible double bond is situated in the chroman nucleus and hence deguelin may be represented by formula (XV ; $R = H$, $R_1 = H$).

According to Clark (*loc. cit.*) tephrosin, $C_{23}H_{22}O_7$, is a hydroxydeguelin which is readily dehydrated, yielding dehydrodeguelin.

In this manner tephrosin resembles rotenolone (LaForge and Smith, *loc. cit.*), with which it is isomeric. By analogy, therefore, with deguelin, tephrosin may be represented by formula (XV; $R = OH$, $R_1 = H$) or (less likely) (XV; $R = H$, $R_1 = OH$), and its oxidation product, tephrosindicarboxylic acid, by formula (XVI).

EXPERIMENTAL.

2-*Carboxyphenoxyacetic Acid.*—A mixture of methyl salicylate (3 g.), ethyl bromoacetate (4 c.c.), anhydrous potassium carbonate (10 g.), and acetone (40 c.c.) was refluxed on the steam-bath for 2 hours. The solution was separated from the potassium salts by filtration and the acetone and excess of ester were removed by evaporation on the steam-bath under diminished pressure. The oily residue, which did not give a coloration with alcoholic ferric chloride, was hydrolysed by boiling for ½ hour with 10% aqueous-alcoholic potassium hydroxide (20 c.c.; 50% alcohol). On isolation the acid crystallised from water in plates (1·5 g.), m. p. 190° after sintering at 185° when placed in a bath at 160° (Found: C, 55·1; H, 4·1. Calc. for $C_9H_8O_5$: C, 55·1; H, 4·1%) (Bischoff, *Ber.*, 1900, **33**, 1398). When ethyl chloroacetate was used in place of the bromo-compound the reaction was incomplete after 12 hours.

2-*Carboxy*-4-*methoxyphenoxyacetic Acid.*—The interaction of methyl 4-*O*-methyl-β-resorcylate (3 g.) with ethyl bromoacetate (4 c.c.) in boiling acetone in the presence of potassium carbonate (7 g.) during 3 hours gave rise to the mixed ester. This compound was hydrolysed by means of a boiling mixture of alcohol (25 c.c.) and 14% aqueous potassium hydroxide (50 c.c.) for ½ hour. The acid crystallised from water in slender needles, m. p. 175° with slight shrinking at 168—170° (Found: C, 53·0; H, 4·6. Calc. for $C_{10}H_{10}O_6$: C, 53·1; H, 4·4%) (compare Perkin and Robinson, J., 1908, **93**, 505).

3 : 4-*Dimethoxyphenoxyacetic Acid.*—In his preparation of 3 : 4-dimethoxyphenol Clark (*J. Amer. Chem. Soc.*, 1931, **53**, 3434) has overlooked the earlier description of this compound by Head and Robertson (J., 1930, 2440). The procedure described by Clark for the nitration of veratrole is inferior to Robinson's method, which gives nitroveratrole in 99% yield (J., 1915, **107**, 257). The reduction of nitroveratrole to the amino-compound is more conveniently carried out with sodium sulphide according to Fargher (J., 1920, **117**, 869) than with tin and hydrochloric acid.

The earlier method for the conversion of aminoveratrole into 3 : 4-dimethoxyphenol has been somewhat modified. The amine (40 g.), dissolved in 10% sulphuric acid (350 c.c.), was diazotised below 0° with sodium nitrite (17 g.). The diazonium solution was treated with charcoal, filtered, and gradually added to a boiling solution of sodium sulphate (100 g., anhydrous) in water (200 c.c.). The formation of the phenol was accompanied by a considerable amount of tar which was only partially soluble in ether. The yield of phenol, twice distilled under reduced pressure, was 18—20% of the theoretical.

A mixture of 3 : 4-dimethoxyphenol (1·5 g.), ethyl bromoacetate (2 c.c.), potassium carbonate (5 g.), and acetone (40 c.c.) was refluxed for 1·5 hours. The hydrolysis of the resulting ester was effected with boiling 10% aqueous-alcoholic potassium hydroxide (50 c.c.). The acid (1·4 g.), m. p. 113—115°, crystallised from benzene in spherical aggregates of rod-like prisms, m. p. 116° (Found in dried material : C, 56·6; H, 5·8. Calc. for $C_{10}H_{12}O_5$: C, 56·6; H, 5·7%). It is readily soluble in warm water and separates from the cooled solution as a hydrate in rectangular prisms. The compound has properties identical with those described by LaForge (*loc. cit.*).

Ethyl 2-*Aldehydo*-4 : 5-*dimethoxyphenoxyacetate* (II).—2-Hydroxy-4 : 5-dimethoxybenzaldehyde (Head and Robertson, *loc. cit.*) (3 g.) readily reacted with ethyl bromoacetate (3 c.c.) in the presence of potassium carbonate (6 g.) in boiling acetone (40 c.c.). After 20 minutes, a sample no longer gave a ferric chloride reaction; this completion of the reaction coincided with the disappearance of the yellow colour which had developed when the reagents were mixed. After isolation the *aldehyde* crystallised from alcohol in almost colourless plates (4 g.), m. p. 129° (Found : C, 58·1; H, 5·9. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%). The compound is sparingly soluble in cold methyl alcohol or acetone and readily reduces warm Fehling's solution and ammoniacal silver nitrate. The semicarbazone crystallised from alcohol in colourless prisms, m. p. 189°.

2-*Carboxy*-4 : 5-*dimethoxyphenoxyacetic Acid* (*Rissic Acid*) (III, R = H).—The foregoing aldehyde (2 g.) was dissolved in warm acetone (50 c.c. at 50°) and oxidised by the careful addition of a solution of potassium permanganate (2·5 g.) in warm water (60 c.c. at 45°). The reaction proceeded slowly and the mixture was finally kept for 20 minutes at room temperature, and cleared with sulphur dioxide. Next day the crystalline *acid-ester* (III, R = Et) (1·5 g.) was collected and on recrystallisation from alcohol formed colourless elongated prisms, m. p. 190° (Found : C, 54·7; H, 5·7. $C_{13}H_{16}O_7$ requires C, 54·9; H, 5·6%).

Hydrolysis of this ester (4 g.) was effected by warm (steam-bath) 6·5% aqueous potassium hydroxide (50 c.c.) during 3 hours. The cooled solution was acidified and next day the solid was collected and crystallised from warm methyl alcohol. Rissic acid formed colourless rod-like prisms which decompose at 257—258° with the evolution of carbon dioxide (Found in dried material: C, 51·5; H, 4·7. Calc. for $C_{11}H_{12}O_7$: C, 51·6; H, 4·7%). This acid is sparingly soluble in the usual organic solvents and in water (Takei and his co-workers, and Clark, *loc. cit.*, record m. p. 256°; LaForge and Smith, *loc. cit.*, m. p. 261—263°).

Treatment of a suspension of the finely powdered acid in ether with excess of diazomethane gave the methyl ester, which crystallised from ether in plates, m. p. 86·5° (Found: C, 54·7; H, 5·6. Calc. for $C_{13}H_{16}O_7$: C, 54·9; H, 5·6%) (Takei and co-workers, *loc. cit.*).

Azlactone of Ethyl 2-Aldehydo-4 : 5-dimethoxyphenoxyacetate (IV).—A mixture of ethyl 2-aldehydo-4 : 5-dimethoxyphenoxyacetate (6 g.), hippuric acid (8 g.), sodium acetate (5 g.), and acetic anhydride (30 c.c.) was heated on the steam-bath for 1·5 hours. 50% Alcohol (100 c.c.) was added to the warm reaction mixture and after several hours the crystalline *azlactone* (7·2 g.) was collected, and recrystallised from alcohol or acetic acid–alcohol, forming elongated, bright orange prisms, m. p. 175° (Found: C, 64·1; H, 5·3. $C_{22}H_{21}O_7N$ requires C, 64·2; H, 5·1%). The compound is sparingly soluble in alcohol or benzene and insoluble in aqueous sodium hydroxide.

Derric Acid (VI).—The foregoing azlactone (12·5 g.) was boiled with a 10% solution of sodium hydroxide (200 c.c.) for 4 hours, and the almost colourless solution saturated with sulphur dioxide (compare Baker and Robinson, J., 1929, 157). After several hours the benzoic acid which had separated was filtered off and the last traces remaining in solution were removed by two extractions with ether. The liquor was then heated on the steam-bath with an excess of concentrated hydrochloric acid for 2 hours, and the *pyruvic acid* (V) gradually separated as a micro-crystalline powder (8 g.). Recrystallised from acetic acid or from a large volume of methyl alcohol, it formed colourless microscopic prisms, m. p. 238° (decomp.) after slight darkening at 220—225° (Found in a specimen dried at 120° in a vacuum: C, 52·3; H, 4·8. $C_{13}H_{14}O_8$ requires C, 52·4; H, 4·7%).

The foregoing pyruvic acid (2·5 g.) was dissolved in 5% aqueous sodium hydroxide and oxidised at room temperature with 30% hydrogen peroxide (3 c.c.). After having been kept for 1 hour, the mixture was warmed to 50° for 15 minutes, cooled, and saturated with sulphur dioxide. Next day the derric acid which had separated in colourless prisms (1·7 g.), m. p. 166—168°, was collected and crystallised from ethyl acetate–ether, forming slender prisms, m. p. 169° (Found: C, 53·3; H, 5·3. Calc. for $C_{12}H_{14}O_7$: C, 53·3; H, 5·2%). The properties of the compound are identical with those of the natural acid (LaForge and Smith, *J. Amer. Chem. Soc.*, 1930, **52**, 1097).

The author is indebted to the Chemical Society for a grant which has in part defrayed the cost of the materials.

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[*Received, February 27th,* 1932.]