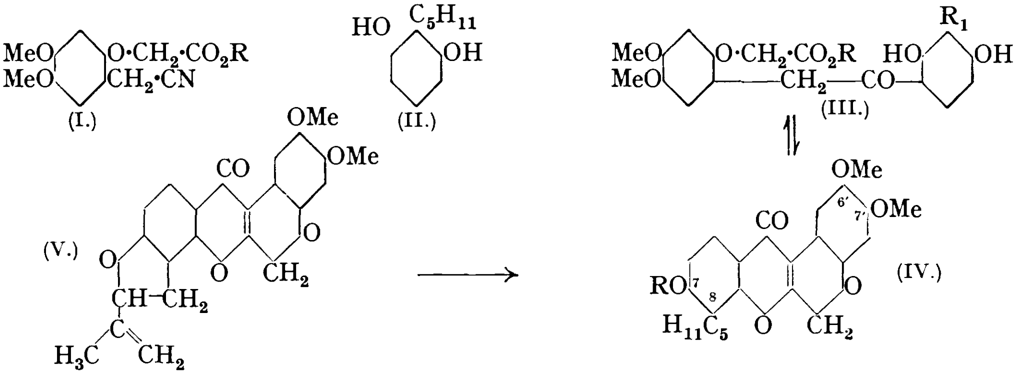
273. *Experiments on the Synthesis of Rotenone and its Derivatives. Part IV. Dehydrodihydrorotenonic Acid and Tephrosic Acid.*

By Alexander Robertson.

On catalytic reduction, dehydrorotenone takes up four atoms of hydrogen, yielding dehydrodihydrorotenonic acid * (La Forge and Smith, *J. Amer. Chem. Soc.*, 1930, **52**, 3608). This compound, like dihydrorotenonic acid which is obtained from rotenone in the same manner, is in reality a phenol (IV; R = H) in which the phenolic group arises by the opening of the dihydrofuran ring of the tubanol residue (La Forge and Haller, *J. Amer. Chem. Soc.*, 1932, **54**, 810). The view regarding the structure of the tubanol residue in (IV; R = H) depended mainly on the fact that Haller and La Forge (*J. Amer. Chem. Soc.*, 1931, **53**, 4460) have shown that tubaic acid on hydrogenation forms a tetrahydro-derivative, which on decarboxylation yields 2 : 6-dihydroxy*iso*amylbenzene (tetrahydrotubanol).

The structure (IV; R = H) previously ascribed to dehydrodihydrorotenonic acid has now been confirmed by the following synthesis according to the general method developed in Part III of this series (this vol., p. 489).



The *nitrile* (I; R = H) was prepared from the *oxime* of 4 : 5-dimethoxyphenoxyacetic-2-pyruvic acid by means of acetic anhydride, and on treatment with diazomethane gave the *ester* (I; R = Me). Condensation of the latter compound and tetrahydrotubanol (II) by the method of Hoesch, and subsequent hydrolysis of the resulting crude ketimine, gave rise to *methyl tetrahydroderrisate* (III; R = Me, $R_1 = iso\text{C}_5\text{H}_{11}$), together with a small amount of derrisic acid; the acid was also obtained quantitatively by the alkaline hydrolysis of the ester. On treatment with boiling acetic anhydride and sodium acetate, the acid (III; R = H, $R_1 = iso\text{C}_5\text{H}_{11}$) furnished the acetate (IV; R = Ac) which on deacetylation gave dehydrodihydrorotenonic acid (IV; R = H). The properties of the synthetic compound and its acetate are identical with those of the natural products.

Taken in conjunction with the following relationships established between dehydrorotenone, dehydrodihydrorotenonic acid, derrisic acid, and tetrahydroderrisic acid by

$$\begin{tikzcd}
\begin{array}{c}\text{Dehydrorotenone}\\ C_{23}H_{20}O_5\end{array} \arrow[r, shift left, "+2H_2O"] \arrow[d, "4H"] & \begin{array}{c}\text{Derrisic acid}\\ C_{23}H_{24}O_8\end{array} \arrow[l, shift left, "-2H_2O"] \arrow[d, "4H"] \\
\begin{array}{c}\text{Dehydrodihydrorotenonic acid}\\ C_{23}H_{24}O_5\end{array} \arrow[r, shift left, "+2H_2O"] & \begin{array}{c}\text{Tetrahydroderrisic acid}\\ C_{23}H_{28}O_8\end{array} \arrow[l, shift left, "-2H_2O"]
\end{tikzcd}$$

La Forge and Haller (*loc. cit.*), the present synthesis of dehydrodihydrorotenonic acid affords conclusive evidence that dehydrorotenone has the chromenochromone structure (V).

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* To avoid confusion the original name for this compound is retained at present (cf. La Forge and Haller, *loc. cit.*).

The route employed for the synthesis of tetrahydrotubanol (II) is identical with that used by Haller (*J. Amer. Chem. Soc.*, 1932, **54**, 4755), the announcement of which appeared without experimental details during the present investigation.

Tephrosic Acid.—The condensation of (I; R = Me) and resorcinol gave rise to tephrosic acid, 4 : 5-dimethoxyphenoxyacetic acid-2-resacetophenone (III; R = H, R_1 = H), thus confirming the structure assigned to this compound by Clark (*J. Amer. Chem. Soc.*, 1932, **54**, 3000; 1933, **55**, 759) and based on the formulæ for tephrosin and tephrosindicarboxylic acid first proposed by the present author (Part II, J., 1932, 1380).

EXPERIMENTAL.

4 : 5-*Dimethoxyphenoxyacetic Acid*-2-*acetonitrile* (I; R = H).—A solution of 4 : 5-dimethoxyphenoxyacetic-2-pyruvic acid (Part III, *loc. cit.*) (8 g.) and hydroxylamine hydrochloride (10 g.) in 10% aqueous sodium hydroxide (80 c.c.) was kept at 50° for 10 minutes, and 24 hours later the *oxime* (11 g.) was precipitated with concentrated hydrochloric acid; it separated from warm water as a hydrate in slender needles, which on being heated melted at 80°, solidified at 105—110°, and then remelted at 160—165°. Dried in a vacuum desiccator, it had m. p. 164—165° (Found : N, 4·5. $C_{13}H_{15}O_8N$ requires N, 4·5%).

After the vigorous reaction between the oxime (10·5 g.) and warm acetic anhydride (20 c.c.) had subsided, the mixture was heated on the steam-bath for 5 minutes, and the excess anhydride decomposed with water (200 c.c.). Next day the yellow crystalline *nitrile* was collected, and on recrystallisation from alcohol (charcoal) formed thick, pale yellow prisms, m. p. 174°, sparingly soluble in warm water, ether, or benzene, and readily soluble in acetone or aqueous sodium bicarbonate (Found : C, 57·5; H, 5·2. $C_{12}H_{13}O_5N$ requires C, 57·4; H, 5·2%). Treatment of a solution of this compound in acetone with a slight excess of ethereal diazomethane gave a quantitative yield of the *methyl* ester (I; R = Me), which separated from aqueous methyl alcohol in masses of long colourless needles, m. p. 92° (Found : C, 58·9; H, 5·7. $C_{13}H_{15}O_5N$ requires C, 58·9; H, 5·7%).

2 : 6-*Dimethoxy*isovalerophenone.—2 : 6-Dimethoxybenzonitrile (Mauthner, *J. pr. Chem.*, 1929, **121**, 259) (140 g.) was added to a solution of *iso*butylmagnesium bromide (from 23 g. of metal and 135 g. of *iso*butyl bromide) in anhydrous ether (800 c.c.), the mixture refluxed for 8 hours, the solvent distilled, and the product thoroughly agitated with dry xylene (400 c.c.) and then heated on the steam-bath for 8 hours. After the removal of the xylene under diminished pressure, the residual solid was treated with water (1 l.) (cool under tap), and the resulting mixture heated on the steam-bath for 2 hours and cooled to 40—45°. Ether (500 c.c.) and then light petroleum (b. p. 40—50°) (800 c.c.) were carefully added to the reaction mixture under reflux, 12 hours later the magnesium hydroxide was dissolved with dilute hydrochloric acid, the crystalline unchanged nitrile removed by filtration, and the light petroleum–ether layer separated, washed with aqueous sodium bicarbonate, dried, and evaporated. The oily residue was refluxed for ¼ hour with light petroleum (b. p. 40—50°) (250 c.c.), and the solution kept at 0° for 12 hours, filtered from a small amount of 2 : 6-dimethoxybenzonitrile, and evaporated, leaving an oil which was practically free from nitrile and on fractionation under reduced pressure gave the *ketone* as a pale straw-coloured oil (40—45 g.), b. p. 178°/15 mm. (Found : C, 70·2; H, 8·2. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·1%). The *semicarbazone* crystallised from alcohol in small, well-formed, colourless prisms, m. p. 207° (Found : N, 15·1. $C_{14}H_{21}O_3N_3$ requires N, 15·1%).

The use of *iso*butyl iodide in place of the bromide sometimes gave less satisfactory results.

2 : 6-*Dihydroxy*isoamylbenzene (*Tetrahydrotubanol*) (II).—A mixture of the foregoing ketone (30 g.), amalgamated zinc (120 g.), concentrated hydrochloric acid (100 c.c.), and water (20 c.c.) was kept for 12 hours and then refluxed for 8 hours. On isolation with ether, tetrahydrotubanol dimethyl ether was separated from higher-boiling impurities by fractionation under diminished pressure, and obtained as a colourless oil (6—7 g.), b. p. 142—145°/15 mm.

A mixture of acetic anhydride (50 c.c.), hydriodic acid (80 c.c., *d* 1·7), and the dimethyl ether (12·5 g.) was refluxed (oil-bath at 140—145°) for 40 minutes, and diluted with excess water. A solution of the crude semi-solid tetrahydrotubanol in ether was washed with aqueous sodium bisulphite, and then with aqueous sodium carbonate, dried, and evaporated. The residual phenol crystallised from light petroleum (b. p. 40—50°) in long colourless needles, m. p. 84°.

4 : 5-*Dimethoxyphenoxyacetic Acid*-2-(2′ : 4′-*dihydroxy*-3′-isoamyl)-*acetophenone* (*Tetrahydroderrisic Acid*) (III; R = H, R_1 = *iso*C_5H_{11}).—A mixture of methyl 4 : 5-dimethoxyphenoxy-

acetate-2-acetonitrile (3·4 g.), tetrahydrotubanol (2·5 g.), fused zinc chloride (3 g.), and anhydrous ether (30 c.c.) was saturated with dry hydrogen chloride (frequently shaken), and during 8 hours the sparingly soluble nitrile and zinc chloride were replaced by a viscous light brown oil. After 4 days, more ether (200 c.c.) was added, the ethereal layer decanted, and the viscous oil washed with ether (3 × 50 c.c). and heated on the water-bath with water (90 c.c.) for 2 hours. Methyl tetrahydroderrisate, which quickly separated, was collected and well ground with aqueous sodium hydrogen carbonate (50 c.c.), washed with water, and crystallised several times from methyl alcohol, forming slender colourless needles (1·5 g.), m. p. 185°, which gave a brownish-red coloration with alcoholic ferric chloride (Found in dried material: C, 64·6; H, 6·8. $C_{24}H_{30}O_8$ requires C, 64·6; H, 6·7%). Hydrolysis of this *ester* (1·2 g.) was effected with 10% aqueous sodium hydroxide containing zinc dust (0·1 g.) on the steam-bath for 35 minutes; the colourless solution gradually darkened. Dilute hydrochloric acid precipitated derrisic acid as a gum (1·0 g.), which separated from 50% alcohol (charcoal) in almost colourless needles, m. p. 214° after recrystallisation from dilute acetic acid and then from 50% alcohol (Found: C, 63·7; H, 6·5. Calc. for $C_{23}H_{28}O_8$: C, 63·9; H, 6·5%) (La Forge and Haller, *loc. cit.*, give m. p. 204—206° and 206°; Butenandt and Hildebrandt, *Annalen*, 1930, **477**, 245, give m. p. 211° for a reduction product of derrisic acid which is in all probability tetrahydroderrisic acid). This compound has a stable ferric chloride reaction identical with that of the methyl ester.

Acidification of the sodium hydrogen carbonate extract of the crude ester gave tetrahydroderrisic acid (0·2 g.).

7-*Acetoxy*-6′ : 7′-*dimethoxy*-8-iso*amylchromeno*-(3′ : 4′ : 2 : 3)-*chromone* (O-*Acetyldehydrodihydrorotenonic Acid*) (IV; R = Ac).—A mixture of tetrahydroderrisic acid (0·7 g.), sodium acetate (0·3 g.), acetic anhydride (10 c.c.), and acetic acid (0·5 c.c.) was refluxed for 12 minutes, cooled to 80°, and diluted with water (10 c.c.) and then with alcohol (15 c.c.). In the course of several hours the acetate (0·3 g.) gradually separated and on recrystallisation from alcohol formed pale yellow prismatic needles, m. p. 202° (Found: C, 68·0; H, 5·8. Calc. for $C_{25}H_{26}O_7$: C, 68·5; H, 5·9%).

7-*Hydroxy*-6′ : 7′-*dimethoxy*-8-iso*amylchromeno*-(3′ : 4′ : 2 : 3)-*chromone* (*Dehydrodihydrorotenonic Acid*) (IV; R = H).—The foregoing acetate (0·2 g.) was boiled with alcohol (20 c.c.) and concentrated hydrochloric acid (4 c.c.) for 10 minutes, and the resulting solution diluted with water (100 c.c.). Dehydrodihydrorotenonic acid gradually separated in characteristic yellow needles, m. p. 215°, and on recrystallisation from 50% alcohol had m. p. 221° (Found, in material dried at 110°: C, 69·7; H, 6·1. Calc. for $C_{23}H_{24}O_6$: C, 69·7; H, 6·1%). This compound is readily soluble in aqueous sodium hydroxide and does not give a ferric chloride reaction. Hydrolysed with aqueous potassium hydroxide according to the directions of La Forge and Haller (*loc. cit.*), it regenerated tetrahydroderrisic acid.

4 : 5-*Dimethoxyphenoxyacetic Acid*-2-*resacetophenone* (*Tephrosic Acid*).—The condensation of methyl 4 : 5-dimethoxyphenoxyacetate-2-acetonitrile (1·5 g.) and resorcinol (4 g.) was effected in anhydrous ether (50 c.c.) with zinc chloride (3 g.) and excess hydrogen chloride. A thick brown oil separated in the course of 3 hours, and after 3 days the remainder of the product was precipitated with ether (100 c.c.), the ethereal layer decanted, and the residual oil washed with ether (2 × 50 c.c.) and heated on the steam-bath with water (70 c.c.) for 2 hours. The product separated in part; the remainder crystallised on cooling. A solution of this solid in aqueous sodium hydrogen carbonate (15 c.c.) was filtered from a small amount of insoluble material (0·15 g.), and, on acidification with hydrochloric acid, deposited tephrosic acid, which separated from 40—50% alcohol in well-formed colourless prisms (0·6 g.) containing solvent of crystallisation, m. p. 197° (Found, in material dried in a high vacuum at 110°: C, 59·4; H, 4·9. Calc. for $C_{18}H_{18}O_8$: C, 59·7; H, 5·0%) (Clark, *loc. cit.*, gives m. p. 196°). With ferric chloride, an alcoholic solution gives a deep wine-red coloration, and an aqueous-alcoholic solution gives a brownish-pink. The material insoluble in sodium hydrogen carbonate gave the same ferric chloride reaction and appeared to be methyl tephrosate. Hydrolysed with warm 10% hydrochloric acid, it formed tephrosic acid, m. p. 197°.

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