46. *Experiments on the Synthesis of Rotenone and its Derivatives. Part VIII. Netoric Acid and Toxicaric Acid.*

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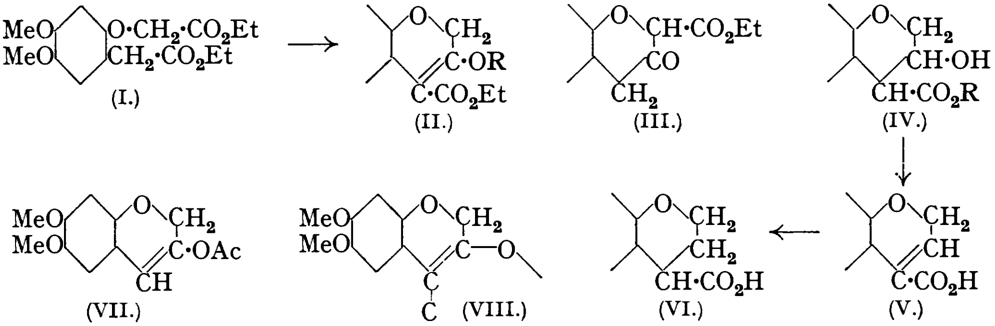
BY the fission of tetrahydrorotenol (dihydrorotenolic acid of older nomenclature) with alkaline hydrogen peroxide, Smith and La Forge (*J. Amer. Chem. Soc.*, 1930, **52**, 4595) obtained a monocarboxylic acid, netoric acid, $C_{12}H_{14}O_5$, m. p. 91—92°, which separated from water as a hydrate (compare Clark, *ibid.*, 1932, **54**, 2537). Subsequently the same compound was prepared from rotenol by Takei and his co-workers (*Ber.*, 1932, **65**, 279) and by Butenandt and McCartney (*Annalen*, 1932, **494**, 17). The former authors considered that the acid formed a hydrate, m. p. 90°, from which they obtained anhydrous material (analysed), m. p. 131—132°, whereas the latter stated that it existed in two interconvertible modifications, m. p. 87 and 131°, giving analytical figures for both forms which are consistent with those of the anhydrous compound.

The application of the same method of degradation to *apo*toxicarol by Clark (*loc. cit.*) and to toxicarol and rotenone by Butenandt and Hilgetag (*Annalen*, 1932, **495**, 172; 1933, **506**, 158) gave an unsaturated acid, toxicaric (dehydronetoric) acid, $C_{12}H_{12}O_5$, which on catalytic reduction readily yielded netoric acid. Under favourable conditions there was simultaneously formed from *apo*toxicarol a hydroxynetoric acid capable of being dehydrated to toxicaric acid. These authors assigned structures (IV, R = H) and (V) to hydroxynetoric and toxicaric acids in accordance with the formula (VI) first proposed for netoric acid by La Forge and his collaborators (*J. Amer. Chem. Soc.*, 1931, **53**, 4400). These structures, which embody the chroman skeleton present in rotenone and toxicarol, have now been independently confirmed by synthetical experiments.



Cyclisation of *ethyl derrate* (I) by means of sodium in warm toluene gave the *ester* (II, R = H), which, since it is a homogeneous crystalline compound instantaneously soluble in dilute aqueous sodium hydroxide, giving a ferric chloride reaction, and readily forming an *acetate*, is obtained in the enolic form. Although this reaction might conceivably have taken an alternative route resulting in the formation of (III), the recognised activity of the methylene group in esters of phenylacetic acids clearly indicates the production of (II, R = H). Further, no trace of a second product could be obtained, a result in agreement with the ring closure of analogous esters recently carried out in these laboratories (unpublished results). Moreover, the subsequent conversion of the enol-ester into netoric acid and toxicaric acid is in keeping with the structure (II, R = H), since, quite apart from the analytical evidence, the synthesis of tetrahydrodehydrorotenone (Robertson, J., 1933, 1163) proves, *inter alia*, the presence of the skeleton (VIII) in rotenone, and under the conditions employed in the degradation this skeleton would not be expected to yield a netoric acid derived from (III).

On reduction in alcohol with hydrogen at atmospheric pressure and a platinum catalyst the enol (II, R = H) yielded the *hydroxy-ester* (IV, R = Et), which on dehydration and subsequent hydrolysis of the crude product gave rise to 6 : 7-dimethoxy-Δ^3-chromene-4-carboxylic acid (V), identical in every way with a specimen of toxicaric acid obtained from toxicarol according to the directions of Butenandt and Hilgetag (*loc. cit.*). This acid was also obtained directly from (IV, R = Et) by alkaline hydrolysis in less favourable yield.

Reduction of the acetate (II, R = Ac) according to the procedure of Roll and Adams (*J. Amer. Chem. Soc.*, 1931, **53**, 3469), followed by hydrolysis of the product, gave rise directly to netoric acid (VI) identical with a natural specimen. This acid (natural and synthetic) has been found to separate from water as the monohydrate, m. p. 90°, which readily loses water of crystallisation and gives the anhydrous form, m. p. 132—133°.

Efforts to convert the ester (II, R = H) into the 6 : 7-dimethoxychroman-3-one by hydrolysis under a number of conditions were unsuccessful, but it was ultimately found that derric acid, on being boiled with sodium acetate and acetic anhydride, gave a product which appears to be the *acetate* (VII) of the enolic form of this chromanone and on deacetylation yielded a solid exhibiting ketonic properties.

EXPERIMENTAL.

Ethyl 3-*Hydroxy*-6 : 7-*dimethoxy*-Δ^3-*chromene*-4-*carboxylate* (II, R = H).—On being boiled with alcohol (100 c.c.) and concentrated sulphuric acid (5 c.c.) for 12 hours, derric acid (10 g.) (Robertson, J., 1932, 1387) gave the *ester* (10 g.), which crystallised from light petroleum (b. p. 60—80°) in colourless needles, m. p. 64°, readily soluble in alcohol or acetone and almost insoluble in water (Found : C, 59·1; H, 6·7. $C_{16}H_{22}O_7$ requires C, 58·9; H, 6·7%).

A solution of this ester (5 g.) in toluene (45 c.c.) containing powdered sodium (0·6 g.) was heated on the steam-bath for 2 hours; the fairly vigorous reaction which started after 10 minutes appeared to be almost complete after ½ hour. The cooled reaction mixture was extracted with three portions of 2% aqueous sodium hydroxide (100, 50, 50 c.c.), the combined extracts were acidified with hydrochloric acid, and 4 hours later the crude *enol-ester* was collected, washed, and dried. The compound was separated from dark-coloured impurities by means of boiling light petroleum (b. p. 60—80°) (charcoal) and then crystallised from the same solvent, forming colourless prisms (2 g.), m. p. 109—110° (Found : C, 60·0; H, 5·7. $C_{14}H_{16}O_6$ requires C, 60·0; H, 5·7%). It is sparingly soluble in cold alcohol, readily soluble in ethyl acetate, benzene, and aqueous sodium hydroxide, and with alcoholic ferric chloride gives a deep blue coloration, destroyed by water and becoming green on standing.

Evaporation of the toluene residues left only traces of unchanged ester.

Acetylation of the compound (1 g.) with acetic anhydride (10 c.c.) and pyridine (5 c.c.) on the steam-bath for ½ hour and then at room temperature for 48 hours gave rise to *ethyl* 6 : 7-*dimethoxy*-3-*acetoxy*-Δ^3-*chromene*-4-*carboxylate* (II, R = Ac), which separated from light petroleum (b. p. 40—60°) in colourless slender needles or diamond-shaped plates, m. p. 84°, readily soluble in alcohol, acetic acid, or benzene (ferric chloride reaction negative) (Found : C, 59·3; H, 5·7. $C_{16}H_{18}O_7$ requires C, 59·6; H, 5·6%).

Ethyl 3-*Hydroxy*-6 : 7-*dimethoxychroman*-4-*carboxylate* (*Ethyl Hydroxynetorate*) (IV, R = Et).—The ester (II, R = H) (1 g.) was hydrogenated in alcohol (500 c.c.) by means of hydrogen at atmospheric pressure and room temperature with the aid of a platinum oxide catalyst (Voorhees and Adams, *J. Amer. Chem. Soc.*, 1922, **44**, 1402) (0·1 g.) in the course of 3 hours (90 c.c. absorbed). Removal of the catalyst and solvent left the *hydroxy-ester* as an oily residue, which gradually solidified and then separated from benzene–light petroleum (b. p. 60—80°) in tufts of colourless slender needles, m. p. 106°, sparingly soluble in ether and readily soluble in benzene or alcohol (Found : C, 59·7; H, 6·2. $C_{14}H_{18}O_6$ requires C, 59·6; H, 6·4%). The ferric chloride reaction was negative.

The reduction did not proceed when ethyl acetate was used as the solvent.

6 : 7-*Dimethoxy*-Δ^3-*chromene*-4-*carboxylic Acid* (*Toxicaric Acid*) (V).—A solution of the aforementioned hydroxy-ester (0·8 g.) in acetic anhydride (4 c.c.) was refluxed for 1·5 minutes, the anhydride decomposed with water (150 c.c.), the aqueous liquor extracted several times with ether, and the combined extracts washed with aqueous sodium bicarbonate. The pale brown oil left on evaporation of the ether was heated on the steam-bath with alcohol (15 c.c.) and water (3 c.c.) containing potassium hydroxide (0·6 g.) for 1 hour and diluted with water (10 c.c.), the greater part of the alcohol was evaporated, and the cooled residue acidified (Congo-red) with hydrochloric acid. Several hours later the brown acid was collected, washed, and crystallised from aqueous acetone (charcoal), forming pale yellow, short, thick or rod-like prisms with square ends, m. p. 210—211° (decomp.), having the properties of natural toxicaric acid (Found: C, 61·2; H, 5·3. Calc. for $C_{12}H_{12}O_5$: C, 61·0; H, 5·1%). Mixed with an

authentic specimen, it showed no depression in the m. p. (Butenandt and Hilgetag, *loc. cit.*, and Clark, *loc. cit.*, give m. p. 210° and 212° respectively).

Hydrolysis of the crude reduction product of the enol-ester (0·5 g.) under the same conditions gave rise to toxicaric acid (0·15 g.), m. p. and mixed m. p. 210—211° (decomp.) after crystallisation from acetone–light petroleum and then aqueous acetone.

In the course of the preparation of toxicaric acid from toxicarol by Butenandt and Hilgetag's method (*loc. cit.*) evaporation of the aqueous-acetone liquors left after crystallisation of the crude toxicaric acid deposited a product, m. p. about 188°, which, when examined under the microscope, appeared to be a mixture of toxicaric acid and hydroxynetoric acid. Treatment of this material with acetic anhydride according to Clark's directions (*loc. cit.*) gave, without further purification, a homogeneous product consisting of almost pure toxicaric acid, m. p. 206° (decomp.).

6 : 7-*Dimethoxychroman*-4-*carboxylic Acid* (*Netoric Acid*) (VI).—Reduction of ethyl 6 : 7-dimethoxy-3-acetoxy-Δ^3-chromene-4-carboxylate (1 g.), dissolved in acetic acid (25 c.c.), was effected with a platinum oxide catalyst (0·1 g.) and hydrogen at room temperature and a pressure of 60 lb./sq. in. in the course of 5 hours. After the separation of the catalyst ice was added, the acetic acid neutralised with sodium carbonate, and the product isolated with ether and hydrolysed by heating with 75% aqueous alcohol (15 c.c.) containing potassium hydroxide (1 g.) on the steam-bath for 1 hour. The mixture was diluted with water (15 c.c.), the greater part of the alcohol evaporated, and the residue acidified with hydrochloric acid. The resulting netoric acid (0·7 g.), which separated in the course of 24 hours, was recrystallised from hot water, forming the hydrate in colourless rods, m. p. 90—91° (rapid heating) (Found in air-dried material: C, 56·3; H, 6·3. Calc. for $C_{12}H_{14}O_5,H_2O$: C, 56·2; H, 6·3%). When slowly heated, this compound loses water with softening at about 90° and then melts sharply at 132—133°. Anhydrous material results when the hydrate is dried for 24 hours over phosphoric oxide in a vacuum at room temperature; m. p. 132—133° (Found : C, 60·8; H, 6·1. Calc. for $C_{12}H_{14}O_5$: C, 60·5; H, 5·9%). The hydrated and the anhydrous form were identical with specimens obtained by the hydrogenation of natural toxicaric acid by means of a platinum oxide catalyst; m. p. and mixed m. p. 90° and 132—133° respectively.

Esterification of the anhydrous acid with excess of ethereal diazomethane gave rise to the methyl ester, which separated from light petroleum (b. p. 40—60°) in clusters of slender needles, m. p. 60—61°, identical with the natural product (Takei and co-workers, *loc. cit.*) (Found : C, 61·9; H, 6·4. Calc. for $C_{13}H_{16}O_5$: C, 61·9; H, 6·4%).

Cyclisation of Derric Acid with Acetic Anhydride.—The acid (1·3 g.) was refluxed with acetic anhydride (20 c.c.) and sodium acetate (2 g.) for 15 minutes, and the pale brown mixture poured into water. Two days later the brownish solid (0·8 g.) was collected, dried, and extracted with warm light petroleum (b. p. 60—80°). The *product*, which slowly separated from the cooled extracts, was crystallised from aqueous methyl alcohol (charcoal) and then light petroleum, forming clusters of colourless slender prisms, m. p. 85° (Found : C, 62·5; H, 5·7. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%). A cooled solution of this compound (0·2 g.) in alcohol (7 c.c.) was mixed with 8% aqueous sodium hydroxide (5 c.c.), kept at 25° for 5 minutes, acidified with dilute hydrochloric acid, and extracted with ether. Evaporation of the ether left a colourless crystalline solid, which in alcoholic solution gave a bright yellow precipitate instantaneously with aqueous dinitrophenylhydrazine hydrochloride (Brady's reagent). This product, which is sparingly soluble in the usual organic solvents, separated from a large volume of hot acetic acid in brownish-orange boat-shaped prisms, decomposing at 203—204°.

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