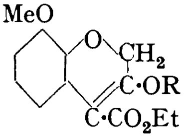
99. *Experiments on the Synthesis of Rotenone and its Derivatives. Part IX.*

By Ronald W. H. O'Donnell, Firmin P. Reed, and Alexander Robertson.

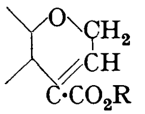
The experiments described in this communication were undertaken in our search of intermediates for preliminary experiments on the synthesis of compounds of the rotenol type and of the chromano-chromanone nucleus of rotenone which appears to be feasible by way of the netoric acid and toxicaric acid types. Although the synthesis of the latter acids proceeded smoothly with comparatively good yields (Part VIII; this vol., p. 212), the difficulty of obtaining the initial materials in quantity led us to explore the preparation of analogous acids. Accordingly, the preparation of 7- and 8-methoxychroman-4-carboxylic acid and of 7- and 8-methoxy-Δ^3-chromene-4-carboxylic acid has now been achieved by the route employed for netoric acid and toxicaric acid and differing from the latter only in experimental details. Because of the poor yields of ethyl 3-hydroxy-Δ^3-chromene-4-carboxylate obtained by cyclisation of ethyl phenoxyacetate-2-acetate (Mr. W. Hilton of this Laboratory, private communication) the investigation of the unsubstituted analogues has not been proceeded with.

Application of the cyanohydrin method (Part VI; J., 1935, 995) to the production of the intermediate *6-methoxyphenoxyacetic-2-acetic acid* gave disappointing results and we returned to a modification of the standard procedure employed for the synthesis of derric acid (Part II; J., 1932, 1380). Attempts to utilise the cyanohydrin route for the preparation of the corresponding resorcinol derivative were also unsuccessful, because, although ethyl 5-methoxy-2-aldehydophenoxyacetate yields a comparatively stable cyanohydrin by the usual methods, efforts to replace the hydroxyl group by chlorine with the aid of thionyl chloride or phosphorus pentachloride in an inert solvent led to the formation of resinous products.

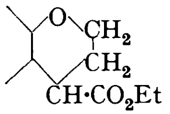
Hydrolysis of esters of the type (IV) with alkali is accompanied by dehydration with the formation of unsaturated acids (type II) (compare Part VIII, *loc. cit.*), but we have also found in the case of (IV; $R = Ac, R_1 = Et$) that hydrolysis with dilute hydrochloric acid gives rise to the *hydroxy-acid* (IV; $R = H, R_1 = H$), an analogue of hydroxynetoric acid. Unlike the *ester* (IV; $R = H, R_1 = Et$), which on being warmed with acetic anhydride gives an almost quantitative yield of the *acetate* (IV; $R = Ac, R_1 = Et$), the acid (IV; $R = H, R_1 = H$) is dehydrated with acetic anhydride–pyridine mixture even at room temperature, forming the *chromeno-acid* (II, $R = H$). Hydrolysis of the *ester* (IV; $R = Ac, R_1 = Et$) with dilute hydrochloric acid might conceivably have given rise to an isomeric acid (V) by a process of dehydration and subsequent hydration, but this possibility is excluded by the fact that on esterification with diazoethane the hydroxy-acid forms the ester (IV; $R = H, R_1 = Et$).



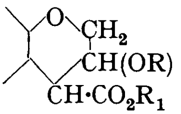
(I.)



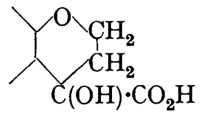
(II.)



(III.)

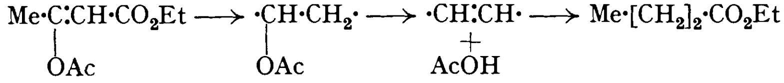


(IV.)



(V.)

The marked difference in the course taken by the enols (compare Michael and Ross, *J. Amer. Chem. Soc.*, **1931**, **53**, 2394) and their acetates on hydrogenation, upon which the success of these syntheses depends, is of some interest and in their memoir on the reduction of enol-acetates Roll and Adams (*ibid.*, p. 3469) suggest that the course of the reaction is as follows:



$$\underset{\mathrm{OAc}}{\mathrm{Me{\cdot}C{:}CH{\cdot}CO_2Et}} \longrightarrow \underset{\mathrm{OAc}}{\mathrm{{\cdot}CH{\cdot}CH_2{\cdot}}} \longrightarrow \underset{\underset{\mathrm{AcOH}}{+}}{\mathrm{{\cdot}CH{:}CH{\cdot}}} \longrightarrow \mathrm{Me{\cdot}[CH_2]_2{\cdot}CO_2Et}$$

Although the reduction of the acetate (I, $R = Ac$) to the chroman-ester (III) proceeds smoothly even at atmospheric pressure, we found that the acetate (IV; $R = Ac, R_1 = Et$) could not be converted directly into (III), and it would therefore appear that, contrary to the suggestion of Roll and Adams, the acetate (IV; $R = Ac, R_1 = Et$) as such is not an intermediate in the conversion of type (I, $R = Ac$) into type (III). Although, as suggested by these authors, there is the possibility of a direct reduction of (I, $R = Ac$) to (III), it may well be that the first stage of this conversion is the extrusion of acetic acid with the formation of (II, $R = Et$), which is immediately hydrogenated to (III).

EXPERIMENTAL.

6-Methoxyphenoxyacetic-2-acetic Acid.—The following procedure gave satisfactory yields of the acid and avoided the troublesome isolation of 6-methoxyphenoxyacetic-2-pyruvic acid (Part VI, *loc. cit.*). A mixture of the azlactone of ethyl 2-aldehydo-6-methoxyphenoxyacetate (20 g.) and 10% aqueous sodium hydroxide (200 c.c.) was refluxed for 4 hours and diluted with water (50 c.c.), and the greater part of the benzoic acid removed with the aid of sulphur dioxide in the usual manner; a small amount of benzoic acid which remained in solution was removed with ether. The aqueous liquor was heated on the steam-bath with concentrated hydrochloric acid (50 c.c.) for 1 hour to decompose the bisulphite compound of the pyruvic acid and to remove dissolved sulphur dioxide; it was then cooled, basified with powdered sodium hydroxide, and treated with 30% hydrogen peroxide (6 c.c., added in the course of 15 minutes with cooling). One hour later the mixture was heated at 50—55° for 20 minutes, and 6-*methoxyphenoxyacetic*-2-*acetic acid* precipitated from the cooled solution by means of sulphur dioxide. Crystallised from warm water, the acid formed diamond-shaped plates (8 g.), m. p. 166°, sparingly soluble in benzene or light petroleum (Found: C, 55·0; H, 5·0. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%). Esterified with alcohol and sulphuric acid, it gave the ethyl ester as a colourless viscous oil, b. p. 198—200°/11 mm. The same ester, mixed with a small amount of free acid, was also obtained by boiling ethyl 6-methoxyphenoxyacetate-2-acetonitrile (10 g., prepared by the cyanohydrin method; Part VI, *loc. cit.*) with alcohol (50 c.c.) and sulphuric acid (25 c.c.), but this route was less satisfactory than the foregoing procedure.

Ethyl 3-*Hydroxy*-8-*methoxy*-Δ^3-*chromene*-4-*carboxylate* (I, R = H).—Cyclisation of the afore-mentioned ester (5 g.) was effected with powdered sodium (0·6 g.) in warm benzene (50 c.c.) in the course of 2 hours. The cooled reaction mixture was treated with water, the benzene separated with the aid of ether, and the aqueous liquor acidified with concentrated hydrochloric acid. Next day the almost pure *product* (2·8 g.) was collected, washed, dried, and crystallised from light petroleum (b. p. 60—80°), forming colourless, stout, rectangular prisms, m. p. 87°, readily soluble in cold aqueous sodium hydroxide and giving a stable royal-blue coloration with alcoholic ferric chloride (Found: C, 62·2; H, 5·8. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%). Prepared by the pyridine–acetic anhydride method, the *acetate* separated from light petroleum (b. p. 40—60°) in colourless prisms, m. p. 72°, with negative ferric reaction (Found: C, 61·7; H, 5·5. $C_{15}H_{16}O_6$ requires C, 61·6; H, 5·5%).

Hydrolysis of the enol-ester with 10% aqueous sodium hydroxide at room temperature for 12 hours gave rise to 6-methoxyphenoxyacetic-2-acetic acid, m. p. and mixed m. p. 166°.

8-*Methoxychroman*-4-*carboxylic Acid*.—Reduction of ethyl 3-acetoxy-8-methoxy-Δ^3-chromene-4-carboxylate (2 g.) was effected in acetic acid (40 c.c.) with hydrogen at 55 lb./sq. in. and a platinum catalyst (Adams) (0·1 g.) in the course of 15 hours. The filtered solution was diluted with water (250 c.c.) and neutralised with sodium carbonate. On isolation with ether the oily product was hydrolysed with 5% ethyl-alcoholic potassium hydroxide (20 c.c.) on the steam-bath for 2 hours and after the addition of water (20 c.c.) the greater part of the alcohol was distilled, and the *acid* precipitated from the cooled residue with concentrated hydrochloric acid. This substance formed clusters of irregular prisms (0·7 g.) from light petroleum (b. p. 80—100°), m. p. 110°, readily soluble in acetone, alcohol, or benzene (Found: C, 63·6; H, 5·7. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8%).

It was subsequently discovered that the reduction of the acetate (1 g.) in acetic acid (20 c.c.) was slowly effected with the same catalyst (0·1 g.) and hydrogen at atmospheric pressure. After isolation and hydrolysis of the product the resulting acid was isolated with ether as a reddish-brown solid, from which pure material (0·2 g.) was obtained by extraction with boiling light petroleum and then crystallisation from same solvent; m. p. and mixed m. p. 110°.

Ethyl 3-*Hydroxy*-8-*methoxychroman*-4-*carboxylate* (IV; R = H, R_1 = Et).—Ethyl 3-hydroxy-8-methoxy-Δ^3-chromene-4-carboxylate (2 g.) was reduced in alcohol (150 c.c.) with hydrogen (200 c.c. absorbed) at atmospheric pressure in the presence of a platinum catalyst (0·15 g.) in 4—6 hours. Evaporation of the filtered solution left the *ester* as a thick viscous oil, which gradually solidified and then separated from light petroleum (b. p. 60—80°) in clusters of rod-like prisms, m. p. 85°, readily soluble in alcohol or benzene, insoluble in aqueous sodium hydroxide, and having a negative ferric reaction (Found: C, 62·3; H, 6·4. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%). Treatment of this compound (2 g.) with acetic anhydride (10 c.c.) at 100° for 2 hours gave the *acetate* (IV; R = Ac, R_1 = Et), which separated from light petroleum (b. p. 40—60°) in irregular prisms (1·9 g.), m. p. 94°, identical with a specimen obtained by acetylation with the aid of pyridine at room temperature [Found: C, 61·6; H, 6·2; $CH_3{\cdot}CO$, 16·3. $C_{13}H_{15}O_5(CO{\cdot}CH_3)$ requires C, 61·2; H, 6·1; $CH_3{\cdot}CO$, 14·6%]. Attempts to reduce this derivative under conditions employed for the preparation of 8-methoxychroman-4-carboxylic acid were unsuccessful; *e.g.*, a solution of the ester (0·5 g.) in acetic acid (10 c.c.) containing an active platinum catalyst (0·1 g.) was agitated in hydrogen at 50 lb./sq. in. for 16 hours. Addition of water to the filtered solution quantitatively precipitated unchanged material, m. p. and mixed m. p. 94°.

3-*Hydroxy*-8-*methoxychroman*-4-*carboxylic Acid* (IV; $R = H$, $R_1 = H$).—Ethyl 3-acetoxy-8-methoxychroman-4-carboxylate (2 g.) was boiled with *N*-hydrochloric acid (30 c.c.) for 1·5 hours, and the resulting solution decanted from a small amount of tarry residue. The *hydroxy-acid* (1 g.) separated from the cooled solution; a further quantity (0·1 g.) was isolated from the acid liquors by means of ether. The compound formed colourless elongated prisms from acetone–light petroleum (b. p. 60—80°), m. p. 197° (decomp.) (Found in a specimen dried in a high vacuum at 100°: C, 59·1; H, 5·4. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%). Esterification of this acid with ethereal diazoethane gave ethyl 3-hydroxy-8-methoxychroman-4-carboxylate, m. p. 85°, identified by comparison with an authentic specimen.

8-*Methoxy*-Δ^3-*chromene*-4-*carboxylic Acid* (II, $R = H$).—Treatment of the foregoing hydroxy-acid (0·5 g.) with acetic anhydride (2 c.c.) and pyridine (1 c.c.) at room temperature for 24 hours gave rise to the *acid*, which separated from benzene or water in almost colourless, slender needles (0·3 g.), m. p. 170° (Found: C, 64·2; H, 5·0. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%). It is readily soluble in alcohol or acetic acid and instantaneously decolorises aqueous potassium permanganate or bromine water. The same acid resulted from the hydrolysis of ethyl 3-hydroxy-8-methoxychroman-4-carboxylate (0·5 g.) or its acetate with aqueous-alcoholic potassium hydroxide (from 0·4 g. of alkali, 2 c.c. of water, and 9 c.c. of alcohol) on the water-bath for 1 hour. The solution was diluted with an equal volume of water, the greater part of the alcohol distilled, and the compound (0·15 g.) precipitated with concentrated hydrochloric acid (cooling); m. p. 170° after crystallisation from water.

5-*Methoxyphenoxyacetic*-2-*acetic Acid*.—After exhaustive purification the initial material, ethyl 2-aldehydo-5-methoxyphenoxyacetate, had m. p. 64° as previously recorded (Part III, J., 1933, 489; Dumont and Kostanecki, *Ber.*, 1909, **42**, 911, give m. p. 68—69°).

This *acid* was prepared by the oxidation of 5-methoxyphenoxyacetic-2-pyruvic acid (Part III, *loc. cit.*) (2·5 g.) in 5% aqueous sodium hydroxide (20 c.c.) with 30% hydrogen peroxide (2 c.c.) and formed colourless prisms (2·0 g.) from warm water, m. p. 163°, readily soluble in alcohol and sparingly soluble in benzene or ethyl acetate (Found: C, 55·0; H, 5·1. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%). The *ethyl* ester was obtained as a crystalline solid, b. p. 178—180°/1 mm., m. p. 37° (Found: C, 61·0; H, 6·8. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%).

Ethyl 3-*Hydroxy*-7-*methoxy*-Δ^3-*chromene*-4-*carboxylate*.—Cyclisation of the afore-mentioned ester (10 g.) was effected with powdered sodium (1·2 g.) in warm benzene (75 c.c.) and on isolation the *product* (4·5 g.) crystallised from warm alcohol in colourless, thick, rectangular prisms, m. p. 62—63°, instantaneously soluble in dilute aqueous sodium hydroxide and giving a Prussian-blue ferric chloride reaction (Found: C, 62·1; H, 5·4. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%). The *acetate*, obtained by means of acetic anhydride and pyridine, formed plates or needles from dilute alcohol, m. p. 51° (Found: C, 61·6; H, 5·5. $C_{15}H_{16}O_6$ requires C, 61·6; H, 5·5%).

7-*Methoxychroman*-4-*carboxylic Acid*.—Reduction of the afore-mentioned acetate (1 g.) in acetic acid (30 c.c.) with hydrogen at 45—50 lb./sq. in. and a platinum catalyst gave a colourless oil, which on hydrolysis with hot 4% alcoholic potassium hydroxide (15 c.c.) for 1½ hours yielded the *acid* as a dark brown oil. This material solidified in the course of 2—3 weeks and then separated from light petroleum (b. p. 40—60°) in colourless irregular prisms (0·3—0·4 g.), m. p. 78°, readily soluble in the usual solvents except light petroleum (Found: C, 63·6; H, 6·0. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8%).

7-*Methoxy*-Δ^3-*chromene*-4-*carboxylic Acid*.—Hydrogenation of ethyl 3-hydroxy-7-methoxy-Δ^3-chromene-4-carboxylate (1 g.) in alcohol (100 c.c.) with hydrogen (approx. 100 c.c. absorbed) at atmospheric pressure and a platinum catalyst (0·1 g.) gave *ethyl* 3-*hydroxy*-7-*methoxychroman*-4-*carboxylate* (1 g.), which formed slender rods from light petroleum (b. p. 60—80°), m. p. 97° (Found: C, 62·2; H, 6·4. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%). This ester (1 g.) was heated with acetic anhydride (6 c.c.) on the steam-bath for 2 hours, and the oily product hydrolysed by being boiled with alcohol (22 c.c.) and water (4 c.c.) containing potassium hydroxide (0·8 g.) for ¾ hour. On isolation the *acid* separated from warm water in almost colourless needles (0·45 g.), m. p. 131°, readily soluble in alcohol and sparingly soluble in benzene or light petroleum (Found: C, 64·2; H, 5·2. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%). This compound instantaneously decolorised aqueous potassium permanganate or bromine water.

We are indebted to the Government Grants Committee of the Royal Society for a grant in aid of this work.

UNIVERSITY OF LIVERPOOL.

[*Received, January 24th*, 1936.]