229. *Experiments on the Synthesis of Rotenone and its Derivatives. Part VI. Chromenochromones.*

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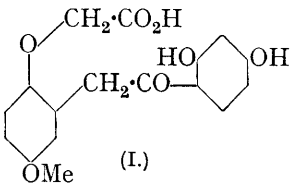
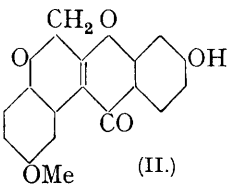
In continuation of studies on the synthesis of compounds of the dehydrorotenone type we have now prepared 7-hydroxy-6′-methoxy- (II), 7-hydroxy-8′-methoxy- (III; R = H, R_1 = H), and 5 : 7 : 8′-trimethoxy-chromeno-(3′ : 4′ : 2 : 3)-chromone (III; R = Me, R_1 = OMe) by way of the intermediate keto-acids (type I) according to the general method developed for the synthesis of tetrahydrodehydrorotenone (dehydrodihydrorotenonic acid) (Part IV; J., 1933, 1163).



(I.)



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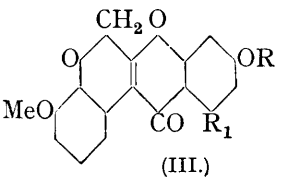
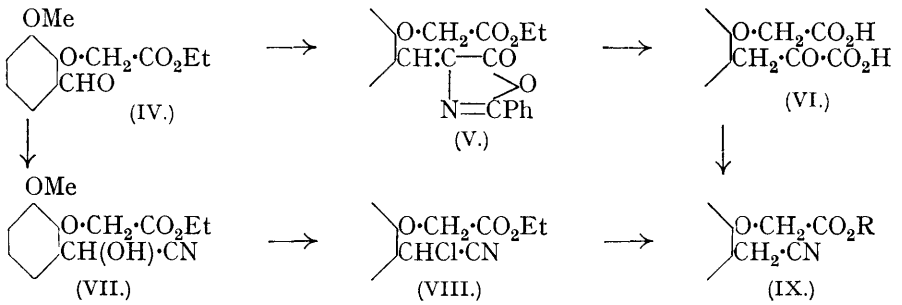


(III.)

In our first attempts to prepare the intermediate *nitrile* (IX, R = H) from the *aldehyde* (IV) by way of the *azlactone* (V) and the pyruvic acid (VI), only traces of the last compound could be isolated. Though this difficulty was eventually avoided by the direct oximation of (VI) in the hydrolytic mixture from (V) after the removal of the benzoic acid, we explored an alternative route to the *nitrile* (IX, R = Et) (compare Hignett and Kay, *J. Soc. Chem. Ind.*, 1935, **54**, 98T).



The cyanohydrin (VII), obtained from (IV), was converted by means of thionyl chloride into the *chloro-nitrile* (VIII), which on reduction with zinc dust and acetic acid yielded the *ester-nitrile* (IX, R = Et). Although this procedure possesses certain obvious advantages over the azlactone route to the required ester-nitrile type (IX), considerable loss of material is liable to occur in the formation of (VIII) owing to the difficulty of obtaining the rather unstable cyanohydrin sufficiently pure and dry. Similar results were obtained in the preparation of ethyl 4-methoxyphenoxyacetate-2-acetonitrile by this route.

Experimental.

Ethyl 2-Aldehydo-4-methoxyphenoxyacetate.—A mixture of 5-methoxysalicylaldehyde (24 g.), ethyl bromoacetate (47 g.), anhydrous potassium carbonate (20 g.), and acetone (200 c.c.)

was refluxed on the water-bath until a sample did not give a ferric chloride reaction; after ½ hour a further quantity of carbonate (15 g.) was added. After the removal of the potassium salts (washed well with acetone) the solvent was evaporated, a solution of the residue in ether was filtered to remove a small amount of residue, the ether evaporated, and the unchanged ethyl bromoacetate removed in a vacuum. Distillation of the product gave the *phenoxyacetate* as a reddish oil (31—32 g.), b. p. 205—206°/18—20 mm., 187—188°/2 mm., which solidified and then crystallised from benzene–light petroleum (b. p. 80—100°) in clusters of colourless needles, m. p. 51°, readily soluble in alcohol (Found: C, 60·8; H, 5·7. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%). The *semicarbazone* separated from alcohol in clusters of colourless needles, m. p. 171° (Found: C, 53·0; H, 5·8. $C_{13}H_{17}O_5N_3$ requires C, 52·7; H, 5·7%).

Azlactone of Ethyl 2-Aldehydo-4-methoxyphenoxyacetate.—The foregoing ester (10 g.) was condensed with hippuric acid (12 g.) by means of sodium acetate (12 g.) and acetic anhydride (40 c.c.) on the water-bath during 1·5 hours, and the cooled mixture carefully treated with alcohol (100 c.c.) and then water (250 c.c.). Next day the *azlactone* was collected and crystallised from alcohol, forming yellow needles (8 g.), m. p. 127° (Found: C, 65·9; H, 5·1. $C_{21}H_{19}O_6N$ requires C, 66·1; H, 5·0%).

4-Methoxyphenoxyacetic Acid-2-acetonitrile.—The azlactone (10·5 g.) was hydrolysed by boiling with 10% aqueous sodium hydroxide (100 c.c.) for 6 hours, and the cooled solution diluted with water (25 c.c.), saturated with a slow stream of sulphur dioxide, and kept for 24 hours. After separation of the benzoic acid the aqueous liquor, on being heated on the water-bath with concentrated hydrochloric acid (25 c.c.) for 2·5 hours, gradually deposited 4-methoxyphenoxyacetic acid-2-pyruvic acid as a microcrystalline powder (6·2 g.). The crude acid (5 g.) was oximated with hydroxylamine hydrochloride (4 g.) in 10% aqueous sodium hydroxide (60 c.c.) maintained at 50—55° for 5 minutes and then at room temperature for 24 hours. The oxime was precipitated with concentrated hydrochloric acid and crystallised from water, forming squat prisms (5 g.), m. p. 150—151°.

As the yield of pyruvic acid sometimes varied, it was subsequently found to be more economical not to isolate this product. After removal of the benzoic acid the filtrate was heated with hydrochloric acid on the water-bath for ½ hour, cooled, basified, and treated with hydroxylamine hydrochloride at 55°; the oxime was isolated as before.

The oxime (4 g.) was warmed on the water-bath with acetic anhydride (13 c.c.) for 10 minutes, the anhydride decomposed with water, and the brownish *acid-nitrile* recrystallised from dilute alcohol (charcoal), forming colourless needles (2 g.), m. p. 140° (Found: C, 60·1; H, 5·2; N, 6·7. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0; N, 6·3%). Esterification of this compound in acetone with ethereal diazomethane gave the *methyl* ester, which separated from benzene–ligroin in prisms, m. p. 45° (Found: C, 61·3; H, 5·6. $C_{12}H_{13}O_4N$ requires C, 61·3; H, 5·5%).

4-Methoxyphenoxyacetic Acid-2-resacetophenone (I).—A mixture of methyl 4-methoxyphenoxyacetate-2-acetonitrile (3 g.), resorcinol (8 g.), zinc chloride (3 g.), and anhydrous ether (150 c.c.) was saturated with hydrogen chloride. 3 Days later the ethereal layer was decanted, and the pink oil washed four times with ether (50 c.c.) and heated on the steam-bath with water (100 c.c.) for 1 hour. The *keto-acid* was isolated from the semi-solid product by means of aqueous sodium bicarbonate and crystallised from dilute alcohol, forming colourless slender needles (2·1 g.), m. p. 121—124°, which appeared to be a hydrate. After having been dried in a high vacuum at 110° over phosphoric oxide, the compound had m. p. 163° (Found: C, 61·6; H, 4·8. $C_{17}H_{16}O_7$ requires C, 61·8; H, 4·8%). It is readily soluble in alcohol or acetone and gives a brownish-red ferric chloride reaction.

7-Hydroxy-6′-methoxychromeno-(3′ : 4′ : 2 : 3)-chromone (II).—Cyclisation of the foregoing keto-acid (1·5 g.) was effected with boiling acetic anhydride (21 c.c.) and sodium acetate (1 g.) in the course of 13 minutes, but, since the previous method (Part IV, *loc. cit.*) of working up the product failed to yield crystalline material, the following procedure was adopted: After being diluted with water (200 c.c.), the reaction mixture was kept for 2 days, and a solution of the resulting gummy precipitate from three experiments (2·7 g. of keto-acid) in alcohol (50 c.c.) was mixed with saturated aqueous sodium bicarbonate (30 c.c.), diluted with water (300 c.c.), and saturated with sodium chloride to hasten the coagulation of the colloidal precipitate. This precipitate, which consisted of impure acetate of the chromone, was boiled with alcohol (50 c.c.) containing dilute hydrochloric acid (10 c.c.) for 10 minutes, and the solution diluted with water. The resulting solid which slowly separated was collected, washed, and extracted with a little hot methyl alcohol. On cooling, the extract deposited the *chromenochromone* (0·2 g.), which on repeated crystallisation from alcohol (charcoal) formed clusters of colourless microscopic needles (0·1 g.), decomposing at 248—249° after slight darkening at 243—245° (Found: C, 68·8;

H, 4·2. $C_{17}H_{12}O_5$ requires C, 68·8; H, 4·1%). The substance does not give a ferric chloride reaction, and forms in concentrated sulphuric acid a pale yellow solution which is non-fluorescent in daylight.

Treatment of the chromenochromone (50 mg.) with acetic anhydride (1·3 c.c.) and pyridine (0·7 c.c.) first on the water-bath for 3 minutes and then at room temperature for 24 hours gave the *acetate*, which separated from alcohol in long colourless needles (30 mg.), m. p. 190° (Found : C, 67·2; H, 4·1. $C_{19}H_{14}O_6$ requires C, 67·5; H, 4·1%).

Ethyl 2-Aldehydo-6-methoxyphenoxyacetate (IV).—This ester was prepared from *o*-vanillin (20 g.), ethyl bromoacetate (35 g.), and potassium carbonate (30 g., added in two portions) in boiling acetone and crystallised from light petroleum (b. p. 60—80°), forming long prisms (28·7 g.), m. p. 75° (Found : C, 60·5; H, 6·1. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%). The *semicarbazone* separated from alcohol in prismatic needles, m. p. 205° (Found : C, 53·0; H, 5·8; N, 14·4. $C_{13}H_{17}O_5N_3$ requires C, 52·7; H, 5·7; N, 14·2%).

Ethyl 6-Methoxyphenoxyacetate-2-chloroacetonitrile (VIII).—The afore-mentioned aldehyde (15 g.) was dissolved with stirring (2 hours) in saturated aqueous sodium hydrogen sulphite (25 c.c.), and the solution treated at 0° with sodium cyanide (5 g.) in water (10 c.c.); agitation was maintained for 3 hours. A washed ethereal solution of the precipitated oil was well dried with sodium sulphate, and the ether distilled, leaving the cyanohydrin (VII) as a pale yellow oil (15 g.).

The addition of aqueous sodium hydrogen sulphite to a mixture of the aldehyde, aqueous sodium cyanide, and ice gave very poor yields of the cyanohydrin.

Thionyl chloride (10 c.c.) was gradually added to a well-cooled solution of the crude cyanohydrin (12 g.) in chloroform (10 c.c.), the mixture kept at room temperature for 4 hours, the solvent and unchanged thionyl chloride removed in a vacuum, and the residual *chloro-nitrile* purified by distillation in a vacuum and then by crystallisation from alcohol or light petroleum, from which it separated in colourless, elongated, rectangular prisms, m. p. 46° (Found : C, 55·1; H, 5·0. $C_{13}H_{14}O_4NCl$ requires C, 55·1; H, 4·9%).

Ethyl 6-Methoxyphenoxyacetate-2-acetonitrile (IX, R = Et).—Zinc dust (2·7 g.) was added in small portions to a hot solution of the foregoing chloro-nitrile (7 g.) in alcohol (8 c.c.), acetic acid (4 c.c.), and water (5 c.c.), and the mixture finally heated on the steam-bath for ½ hour. After filtration the alcohol was evaporated, the residue treated with dilute hydrochloric acid, and the nitrile (5 g.) isolated with ether. Crystallised from 50% alcohol, it formed rectangular prisms, m. p. 53° (Found : C, 62·8; H, 6·1; N, 5·7. $C_{13}H_{15}O_4N$ requires C, 62·7; H, 6·0; N, 5·6%).

Considerable loss of material resulted when the crude chloro-nitrile was distilled and in subsequent experiments the crude product was reduced; yield, 19 g. of nitrile from 30 g. of ethyl 2-aldehydophenoxyacetate.

6-Methoxyphenoxyacetic Acid-2-acetonitrile (IX, R = H).—The *azlactone* of ethyl 2-aldehydophenoxyacetate was prepared from the aldehyde (20 g.) and hippuric acid (25 g.) with the aid of warm sodium acetate (25 g.) and acetic anhydride (90 c.c.). Crystallised from dilute alcohol, it formed elongated yellow prisms (18 g.), m. p. 126° (Found : C, 66·0; H, 5·2; N, 3·9. $C_{21}H_{19}O_6N$ requires C, 66·1; H, 5·0; N, 3·7%).

The azlactone (20 g.) was boiled with 10% aqueous sodium hydroxide (200 c.c.) for 4 hours, the cooled solution saturated with sulphur dioxide, 24 hours later the precipitated benzoic acid was removed, and after the addition of concentrated hydrochloric acid (50 c.c.) the mixture was heated on the water-bath for ½—1 hour to decompose the bisulphite compound of 6-methoxyphenoxyacetic acid-2-pyruvic acid and to remove the sulphur dioxide. The liquor was then basified with powdered sodium hydroxide and mixed with hydroxylamine hydrochloride (10 g.) at 50—55°. Next day the solution was filtered to remove a small amount of solid, and the *oxime* (14 g.) precipitated with hydrochloric acid; m. p. 164° after crystallisation from warm water (Found : N, 5·2. $C_{12}H_{13}O_7N$ requires N, 5·0%).

The air-dried oxime (6 g.) was digested on the steam-bath with acetic anhydride (18 c.c.), the excess of anhydride was decomposed with water (200 c.c.), and 48 hours later the *acid-nitrile* was collected; a further quantity was obtained by saturating the mother-liquor with ammonium sulphate. Crystallised from dilute alcohol, the compound formed colourless rods (2·6 g.), m. p. 93° (Found : C, 60·0; H, 4·9. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0%). The ethyl ester, prepared by means of ethereal diazoethane, separated from aqueous alcohol in rectangular prisms, identical with a specimen prepared by the cyanohydrin method; m. p. and mixed m. p. 53° (Found : C, 62·4; H, 6·1%).

6-Methoxyphenoxyacetic Acid-2-resacetophenone.—The ester of the foregoing nitrile (5 g.)

was condensed with resorcinol (13 g.) in ether (100 c.c.) with zinc chloride (5 g.) and excess of hydrogen chloride. After 4 days the ethereal layer was decanted, and the thick brown oil washed with ether (3 × 50 c.c.) and then heated on the steam-bath with water (100 c.c.) for 2 hours. Next day the *keto-acid* was isolated from the semi-solid product by means of aqueous sodium bicarbonate, leaving a residue of impure ethyl ester, and, on crystallisation from ethyl acetate and then from aqueous acetone, formed colourless prisms (0·72 g.), m. p. 180·5°, which gave a wine-red coloration with alcoholic ferric chloride (Found: C, 61·6; H, 4·9. $C_{17}H_{16}O_7$ requires C, 61·8; H, 4·8%).

Hydrolysis of the sodium bicarbonate-insoluble ester with 10% hydrochloric acid (agitate), or with 8% aqueous sodium hydroxide containing a little zinc dust, on the water-bath for 2 hours gave a further quantity of the keto-acid (2·3 g.).

7-Hydroxy-8′-methoxychromeno-(3′ : 4′ : 2 : 3)-chromone (III; R = H, R_1 = H).—A mixture of 6-methoxyphenoxyacetic acid-2-resacetophenone (1·8 g.), sodium acetate (1 g.), and acetic anhydride (28 c.c.) was refluxed for 20 minutes, cooled, and mixed with alcohol (25 c.c.). On the addition of water (50 c.c.) the *acetate* of the chromenochromone gradually separated in yellow microscopic crystals and on recrystallisation from alcohol formed slender colourless needles (0·6 g.), m. p. 196° (Found: C, 67·2; H, 4·3. $C_{19}H_{14}O_6$ requires C, 67·5; H, 4·2%).

Hydrolysis of the acetate (0·3 g.) was effected with boiling alcohol (20 c.c.) containing concentrated hydrochloric acid (3 c.c.) during 10 minutes, and the *chromenochromone* precipitated with water. Crystallised from alcohol (charcoal), it formed almost colourless needles, m. p. 263—265° (decomp.), and did not give a ferric chloride reaction (Found: C, 68·8; H, 4·0. $C_{17}H_{12}O_5$ requires C, 68·8; H, 4·1%).

Condensation of Ethyl 6-Methoxyphenoxyacetate-2-acetonitrile with Phloroglucinol Dimethyl Ether.—A mixture of the nitrile (3 g.), phloroglucinol dimethyl ether (7 g.), zinc chloride (3 g.), and ether (100 c.c.) saturated with hydrogen chloride was kept for 7 days, the ethereal layer decanted, and the residual red-brown oil washed with ether (3 × 50 c.c.) and heated on the steam-bath with water (100 c.c.) for 2 hours. The resulting semi-solid was heated with 8% hydrochloric acid (50 c.c.) for 2 hours, and the mixture of isomeric keto-acids isolated with aqueous sodium bicarbonate. On treatment with warm hydrochloric acid the residue insoluble in aqueous sodium bicarbonate gave a further quantity of the keto-acids.

The mixed keto-acids were extracted four times with boiling benzene (25 c.c.), and the combined extracts evaporated, leaving 6-methoxyphenoxyacetic acid-2-2′ : 4′-*O*-dimethylphloracetophenone, which separated from aqueous methyl alcohol as a *hydrate* in irregular plates (0·8 g.), m. p. 143—144° (Found: C, 57·4; H, 5·3. $C_{19}H_{20}O_8,H_2O$ requires C, 57·7; H, 5·5%). The compound gives a red-brown ferric chloride reaction.

The residue insoluble in benzene consisted of the isomeric 2′ : 6′-O-*dimethyl* ether, which crystallised from dilute alcohol in plates (0·5 g.), m. p. 174°, and did not give a ferric chloride reaction (Found: C, 60·5; H, 5·5. $C_{19}H_{20}O_8$ requires C, 60·6; H, 5·3%).

5 : 7 : 8′-Trimethoxychromeno-(3′ : 4′ : 2 : 3)-chromone (III; R = Me, R_1 = OMe).—Cyclisation of 6-methoxyphenoxyacetic acid-2-2′ : 4′-*O*-dimethylphloracetophenone (1 g.) was effected with boiling acetic anhydride (15 c.c.) and sodium acetate (0·6 g.) during 15 minutes, and the anhydride decomposed with water (250 c.c.). An alcoholic solution (50 c.c.) of the gummy product from two experiments was mixed with aqueous sodium carbonate (50 c.c.) and diluted with water (500 c.c.). The colloidal precipitate of the crude *chromenochromone* was coagulated by saturating the liquor with sodium chloride, collected, washed with water, and crystallised several times from alcohol, forming almost colourless needles (30 mg.), m. p. 210° (Found: C, 66·8; H, 4·7. $C_{19}H_{16}O_6$ requires C, 67·1; H, 4·7%).

Preparation of Ethyl 4-Methoxyphenoxacetate-2-acetonitrile by the Cyanohydrin Method.—The solid bisulphite compound of ethyl 2-aldehydo-4-methoxyphenoxyacetate (6 g.) was dissolved in the minimum amount of water and treated at 0° with sodium cyanide (3 g.), and the solid cyanohydrin (6 g.), m. p. 61—63°, collected, dried, and converted into the chloro-nitrile by means of thionyl chloride in chloroform. The crude product was reduced with zinc dust (2·5 g.), acetic acid (3 c.c.), and water (4 c.c.), and ethyl 4-methoxyphenoxyacetate-2-acetonitrile (2·5 g.) isolated by means of ether. Crystallised once from dilute alcohol, it had m. p. 121—122°, and on condensation with resorcinol by the method used in the case of the corresponding methyl ester gave 4-methoxyphenoxyacetic acid-2-resacetophenone, m. p. and mixed m. p. 163°.

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