122. *Experiments on the Synthesis of Rotenone and its Derivatives. Part III. The Dehydrorotenone Nucleus.*

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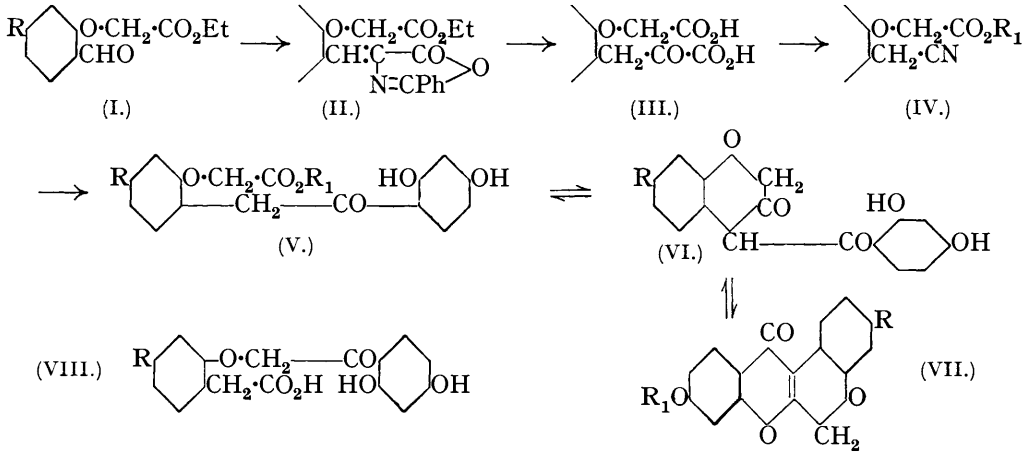
THE formulæ proposed for dehydrorotenone by La Forge (*J. Amer. Chem. Soc.*, 1932, **54**, 810) and for dehydrodeguelin by the present author (Part II, J., 1932, 1380; cf. Clark, *J. Amer. Chem. Soc.*, 1932, **54**, 3000, and Butenandt and Hilgetag, *Annalen*, 1932, **495**, 172) embrace a chromenochromone nucleus of the type (VII), and the formation of the phenolic acids, derrisic and deguelic (type V), from these compounds by means of alkalis is considered to be due to the opening of this ring system, probably by way of the stage (VI). The analogous *iso*- and tetrahydro-compounds which contain a modified tubanol residue behave in a similar manner. Conversely, on dehydration with acetic anhydride and sodium acetate these phenolic acids have been shown to re-form the chromenochromone nucleus (compare La Forge, *loc. cit.*).

Chromones of the type (VII) have not been prepared previously and the experiments described in the present memoir represent the successful outcome of an extensive investigation which was undertaken in order to explore a route suitable for the synthesis of such substances, and to compare their properties with those of the natural dehydrorotenone series, the structures of which depend entirely on analytical evidence. In the first instance, on account of the labour involved in preparing quantities of 2-hydroxy-4 : 5-dimethoxybenzaldehyde the more accessible 4-*O*-methylresorcylaldehyde was used as the initial material.

The condensation of the *aldehydophenoxy-ester* (I, R = OMe) with hippuric acid in the usual manner yielded the *azlactone* (II, R = OMe) and on hydrolysis this substance gave rise to the *pyruvic acid* (III, R = OMe), the *oxime* of which was converted into the *nitrile* (IV, R = OMe; R_1 = H) by means of acetic anhydride. Condensation of the *ester* (IV, R = OMe; R_1 = Me) with resorcinol according to the well-known method of Hoesch afforded an oily ketimine double compound which on hydrolysis furnished a mixture of the *keto-acid* (V, R = OMe; R_1 = H) and its *methyl* ester (V, R = OMe; R_1 = Me) (prolonged hydrolysis decreases the amount of ester). The fact that the ester group survives the Hoesch reaction affords ample evidence that the final product has the structure (V) and not the alternative (VIII, R = OMe); a compound having the latter formula might conceivably have been formed under the conditions employed.



Under conditions strictly comparable with those required for the conversion of derrisic acid into dehydrorotenone, *viz.*, treatment with boiling acetic anhydride and sodium acetate, the ketonic acid (V, R = OMe; R_1 = H) gave rise to the *acetate* of the chromone (VII, R = OMe; R_1 = Ac), which on deacetylation with warm alcoholic hydrochloric acid yielded the *chromone* (VII, R = OMe; R_1 = H). Although it has not been possible to isolate an intermediate product in the cyclisation reaction, it seems reasonable to suppose that the formation of the diketone (VI) is an intermediate step in this process. On hydrolysis with alkali the chromone (VII, R = OMe; R_1 = H) and its acetate re-formed the ketonic acid (V, R = OMe; R_1 = H), and by analogy with the scission of the simpler chromones this reaction in all probability proceeds by way of the stage (VI). This reaction is identical with the formation of derrisic acid and deguelic acid from dehydrorotenone and dehydrodeguelin respectively.

In a similar manner the synthesis of 7-*acetoxychromeno*-(3′ : 4′ : 2 : 3)-*chromone* was effected by way of the *acid* (V, R = H; R_1 = H).

An alternative route which appeared to be suitable for the preparation of nitriles of the type (IV) is the etherification of *o*-hydroxyphenylacetonitriles with ethyl bromoacetate. This was tested with *o*-hydroxyphenylacetonitrile, but owing to the small yields obtained in the preparation of this nitrile the procedure appears to be inferior to the one already described.

Experimental.

Ethyl 2-Aldehydo-5-methoxyphenoxyacetate (I, R = OMe).—A mixture of 4-*O*-methylresorcylaldehyde (11 g.), ethyl bromoacetate (15 c.c.), well-ground K_2CO_3 (15 g.), and acetone (70 c.c.) was refluxed until a sample of the product did not give a reaction with alc. $FeCl_3$ (1·5—2 hr.). The filtered solution was evaporated, and the *aldehydo*-ester separated from unchanged ethyl bromoacetate by distillation in a vac., b. p. 220—230°/15 mm., and crystallised from light petroleum (b. p. 40—60°), forming clusters of prismatic needles (12 g.), m. p. 64° (Found: C, 60·3; H, 5·9. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%). It is readily sol. in EtOH, C_6H_6 or acetone, and does not give a $FeCl_3$ reaction. The *semicarbazone* separated from warm EtOH–AcOH in clusters of tiny rectangular plates, m. p. 222° (Found: C, 52·9; H, 6·1. $C_{13}H_{17}O_5N_3$ requires C, 52·7; H, 5·7%).

Azlactone of Ethyl 2-Aldehydo-5-methoxyphenoxyacetate (II, R = OMe).—The condensation of the ester (2·4 g.) and hippuric acid (3 g.) was effected with Ac_2O (10 c.c.) and AcONa (3 g.) on the steam-bath during 1 hr. EtOH (25 c.c.) and then H_2O (30 c.c.) were added gradually to the warm reaction mixture, and next day the *azlactone* was collected and recrystallised from EtOH, forming bright yellow, slender needles (2·4 g.), m. p. 128—129° (Found: C, 65·8; H, 5·1. $C_{21}H_{19}O_6N$ requires C, 66·1; H, 5·0%).

5-Methoxyphenoxyacetic-2-pyruvic Acid (III, R = OMe).—A mixture of the foregoing azlactone (21 g.) and 10% aq. NaOH (20 c.c.) was refluxed for 6 hr., diluted with H_2O (50 c.c.), and saturated with SO_2. Next day the benzoic acid thus pptd. was filtered off (wash with 50 c.c. of H_2O), and the liquor heated on the water-bath with an excess of HCl aq. for 3 hr. The *pyruvic acid* gradually separated as a microcryst. powder (12 g.) and, on recrystn. from a large vol. of AcOH, was obtained in almost colourless, diamond-shaped plates, m. p. 250—251° (decomp.) (Found in material dried in a high vac. at 120°: C, 53·3; H, 4·5. $C_{12}H_{12}O_7$ requires C, 53·7; H, 4·5%). This compound is sparingly sol. in the usual org. solvents.

5-Methoxyphenoxyacetic Acid-2-acetonitrile (IV, R = OMe; R_1 = H).—A solution of hydroxylamine hydrochloride (8 g.) and 5-methoxyphenoxyacetic-2-pyruvic acid (10 g.) in 10% aq. NaOH (120 c.c.) was warmed at 50—55° for 5 min. and 24 hr. later addition of conc. HCl (Congo-red) pptd. the oxime (11 g.), which was collected, washed, and air-dried. Recryst. from warm H_2O, it separated as an *anhydro*-form in colourless slender needles, which on being heated melted at 128—130°, became cryst. at 140—145° (elongated prisms), and finally melted at 152—153° (Found in material dried over P_2O_5 in a vac. desiccator: C, 53·5; H, 4·6. $C_{12}H_{11}O_6N$ requires C, 54·0; H, 4·2%. $C_{12}H_{13}O_7N$ requires C, 50·9; H, 4·6%). The anhydroform is much less sol. in H_2O than the crude air-dried material.

The crude air-dried oxime (7 g.) was warmed with Ac_2O (20 c.c.) on the water-bath and, when the vigorous reaction had abated, H_2O (200 c.c.) was added. 12 Hr. later the brown cryst. *nitrile* was collected, well washed with H_2O, and recrystallised from dil. EtOH (charcoal), forming colourless needles (4 g.), m. p. 156°, readily sol. in aq. $NaHCO_3$ (Found: C, 59·8; H, 5·2. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0%). Addition of an excess of ethereal diazomethane to a solution of the nitrile in acetone gave rise to the *methyl* ester, which separated from 60% aq. MeOH in elongated prisms, or from C_6H_6–ligroin in glistening plates, m. p. 88° (Found: C, 61·2; H, 5·5. $C_{12}H_{13}O_4N$ requires C, 61·3; H, 5·5%). This compound is readily sol. in EtOH or C_6H_6 and sparingly sol. in Et_2O.

5-Methoxyphenoxyacetic Acid-2-resacetophenone (V, R = OMe; R_1 = H).—A mixture of methyl 5-methoxyphenoxyacetate-2-acetonitrile (3 g.), resorcinol (8 g.), $ZnCl_2$ (3 g.), and dry Et_2O (150 c.c.) was saturated with a slow stream of HCl. The mixture was occasionally shaken and in the course of 2 hr. the sparingly sol. nitrile and $ZnCl_2$ were gradually replaced by a viscous reddish-brown oil. 4 Days later the ethereal layer was decanted, and the oily residue washed with Et_2O (3 × 50 c.c.) and heated on the steam-bath with H_2O (80 c.c.) for ½ hr. On cooling, the semi-solid product was collected, washed with H_2O, and extracted with aq. $NaHCO_3$, leaving an insol. residue. Acidification of the filtered extract threw down *5-methoxyphenoxyacetic acid-2-resacetophenone* as an oil which gradually solidified. This compound separated from 20% aq. EtOH as a *hydrate* in almost colourless needles (2 g.), m. p. 193° (Found in specimen dried over H_2SO_4 in a desiccator: C, 58·4; H, 5·2. $C_{17}H_{16}O_7,H_2O$ requires C, 58·3; H, 5·1%. Found in material dried at 110° in a high vac.: C, 61·4; H, 4·8. $C_{17}H_{16}O_7$ requires C, 61·8; H, 4·8%). It is readily sol. in MeOH, EtOH, or AcOH, and with alc. $FeCl_3$ gives a brownish-red coloration.

The material insol. in aq. $NaHCO_3$ consisted of the *methyl* ester of the keto-acid, which separated from C_6H_6 in clusters of short prisms, m. p. 89—90° (Found: C, 62·3; H, 5·3. $C_{18}H_{18}O_7$ requires C, 62·4; H, 5·2%). With alc. $FeCl_3$ this substance gives a wine-red coloration

which becomes red-brown on dilution with H_2O. On hydrolysis with hot 10% HCl at 100° for 2 hr. (agitate) it gave rise to the acid, m. p. and mixed m. p. 193°, after crystn. from dil. EtOH (Found in dried specimen : C, 61·6; H, 4·9%).

7-Hydroxy-7'-methoxychromeno-(3' : 4' : 2 : 3)-chromone (VII, R = OMe; R_1 = H).—The foregoing keto-acid (0·5 g.) was refluxed with Ac_2O (7 c.c.) and AcONa (0·3 g.) for 10 min., and on the addition of EtOH (7 c.c.) and then H_2O (12 c.c.) to the cooled mixture the *acetate* of 7-hydroxy-7'-methoxychromeno-(3' : 4' : 2 : 3)-chromone separated as a brownish cryst. solid in the course of several hr. Recryst. from EtOH (charcoal), it formed almost colourless needles, m. p. 195° (Found in material dried in a high vac. : C, 67·2; H, 4·2. $C_{19}H_{14}O_6$ requires C, 67·5; H, 4·1%). This compound is insol. in aq. NaOH, and does not give a $FeCl_3$ reaction. Mixed with the original ketone, it melted at 170—175°.

A mixture of EtOH (20 c.c.) and conc. HCl (5 c.c.) containing a suspension of the acetate (0·7 g.) was refluxed for 10 min., and the cooled solution diluted with H_2O (100 c.c.). 12 Hr. later the *chromone* was collected, washed, and crystallised from 80% aq. EtOH, forming clusters of almost colourless microscopic prisms, m. p. 258—260° (decomp.) (Found in material dried at 110° in a high vac. : C, 68·8; H, 4·2. $C_{17}H_{12}O_5$ requires C, 68·8; H, 4·1%). This compound is more sol. in MeOH, EtOH, and AcOH than the acetyl derivative. It dissolves readily in dil. aq. NaOH, but does not give a $FeCl_3$ reaction.

A solution of the hydroxychromone (0·2 g.) in 10% aq. NaOH (10 c.c.) was refluxed for 1 hr. and the light brown ppt. obtained on acidification with dil. HCl was collected, washed, and dissolved in aq. $NaHCO_3$. After filtration from a trace of insol. material, the addition of dil. HCl repptd. almost pure 5-methoxyphenoxyacetic acid-2-resacetophenone, which separated from aq. EtOH in colourless needles, m. p. and mixed m. p. 193°, identical in every way with an authentic specimen. Treatment of the acetate of the chromone with aq.-alc. NaOH in a similar manner gave the same compound.

Ethyl 2-Aldehydophenoxyacetate (I, R = H).—A mixture of salicylaldehyde (25 c.c.), ethyl bromoacetate (35 c.c.), K_2CO_3 (20 g.), and acetone (100 c.c.) was refluxed for 2 hr.; after ½ hr. a further quantity of K_2CO_3 (10 g.) was added. The solution was separated from the potassium salts by filtration (wash with acetone) and the solvent and the excess of ethyl bromoacetate were removed by evaporation on the steam-bath under diminished press. Distillation of the oily residue gave the *ester* as a colourless solid, b. p. 195—197°/23 mm., m. p. 34—35° (Found : C, 63·4; H, 5·9. $C_{11}H_{12}O_4$ requires C, 63·2; H, 5·7%). The compound, which was readily sol. in EtOH or C_6H_6 and sparingly sol. in ligroin, did not give a $FeCl_3$ reaction. The *semicarbazone* separated from EtOH in needles, m. p. 178° (Found : C, 54·2; H, 5·7. $C_{12}H_{15}O_4N_3$ requires C, 54·3; H, 5·7%).

The condensation of this aldehyde (22 g.) and hippuric acid (40 g.) was effected with Ac_2O (100 c.c.) and AcONa (20 g.) on the steam-bath during 1·5 hr. Excess H_2O pptd. the *azlactone*, which was collected 2 days later and recrystallised from EtOH, forming slender, canary-yellow needles (20 g.), m. p. 131° (Found : C, 68·4; H, 4·8. $C_{20}H_{17}O_5N$ requires C, 68·4; H, 4·8%).

Phenoxyacetic acid-2-acetonitrile (IV, R = H; R_1 = H).—The aforementioned azlactone (20 g.) was hydrolysed with boiling 10% aq. NaOH for 5 hr., and the pyruvic acid (10 g.) separated from the benzoic acid and isolated by the method employed in the case of 5-methoxyphenoxyacetic acid-2-pyruvic acid. On treatment with hydroxylamine hydrochloride (6 g.) and 10% aq. NaOH (50 c.c.) the crude compound (5 g.) was converted into the oxime, which separated from warm H_2O in clusters of colourless needles.

On being warmed on the steam-bath a mixture of the dry oxime (3·6 g.) and Ac_2O (10 c.c.) reacted vigorously and after 10 min. the excess of Ac_2O was decomposed with H_2O. Next day *phenoxyacetic acid-2-acetonitrile* was pptd. by means of $(NH_4)_2SO_4$, collected, washed, dried, and crystallised from C_6H_6, forming thick prisms (2·2 g.), m. p. 136° after sintering at 130° (Found : C, 62·9; H, 4·8. $C_{10}H_9O_3N$ requires C, 62·8; H, 4·7%). The compound is readily sol. in EtOH, AcOH, or Et_2O and sparingly sol. in ligroin. On treatment with ethereal diazomethane it formed the *methyl* ester, which separated from C_6H_6–light petroleum (b. p. 50—60°) and then from dil. MeOH in elongated glistening plates, m. p. 68° (Found : N, 7·1. $C_{11}H_{11}O_3N$ requires N, 6·8%).

Phenoxyacetic acid-2-resacetophenone (V, R = H; R_1 = H).—A solution of methyl phenoxyacetate-2-acetonitrile (3 g.) and resorcinol (4. g.) in Et_2O (50 c.c.) was saturated with dry HCl in the presence of $ZnCl_2$ (3 g.), and a thick brown oil gradually separated. 3 Days later the remainder of the product was pptd. with Et_2O (100 c.c.), the ethereal layer decanted, and the viscous syrup washed with Et_2O (4 × 25 c.c.). A solution of the product in H_2O (100 c.c.) was heated on the steam-bath for 2 hr. and next day the solid was collected, washed, and dis-

solved in aq. $NaHCO_3$. The solution was filtered to remove insol. material (0·5 g.), and, on being repptd. with dil. aq. HCl, the *ketone* was obtained as an oil which soon solidified. Recryst. from dil. MeOH, it formed slender needles (1·9 g.), m. p. 206° (Found in material dried at 110°: C, 63·7; H, 5·0. $C_{16}H_{14}O_6$ requires C, 63·6; H, 4·6%). This compound is readily sol. in EtOH and AcOH and gives with alc. $FeCl_3$ a dark red coloration. The material insol. in aq. $NaHCO_3$ gave a wine-red $FeCl_3$ reaction and appeared to be the ester of the keto-acid. On hydrolysis with dil. HCl on the steam-bath it formed the acid.

7-*Acetoxychromeno*-(3′ : 4′ : 2 : 3)-*chromone* (VII, R = H; R_1 = Ac).—A mixture of the foregoing keto-acid (0·9 g.), Ac_2O (15 c.c.), AcOH (1 c.c.), and AcONa (0·3 g.) was refluxed for 30 min., cooled, and diluted with EtOH (10 c.c.) and then with H_2O (20 c.c.). The *chromone* gradually separated in clusters of light brown rods, and on recrystn. from EtOH (charcoal) and then from AcOH–EtOH formed colourless needles, m. p. 178° (Found: C, 69·9; H, 4·0. $C_{18}H_{12}O_5$ requires C, 70·1; H, 3·9%). It is sparingly sol. in MeOH, EtOH, or C_6H_6, and does not give a $FeCl_3$ reaction.

Treatment of this compound with boiling aq.-alc. NaOH in the manner described in the case of 7-acetoxy-7′-methoxychromeno-(3′ : 4′ : 2 : 3)-chromone re-formed the keto-acid (V, R = H; R_1 = H), m. p. and mixed m. p. 206° after crystn. from dil. MeOH.

2-*Hydroxyphenylacetonitrile*.—A solution of 3-hydroxycoumarin (Erlenmeyer, *Annalen*, 1905, **337**, 289) (10 g.) in 10% aq. NaOH was boiled for 5 min., cooled to 50°, and treated with hydroxylamine hydrochloride (9 g.). Next day the *oxime* (10 g.) of 2-hydroxyphenylpyruvic acid was pptd. with conc. HCl, and on crystn. from H_2O and then from C_6H_6 formed colourless needles, m. p. 126° (decomp.) after sintering at 120° (Found: C, 55·7; H, 5·0. $C_9H_9O_4N$ requires C, 55·4; H, 4·6%). This compound is sol. in aq. $NaHCO_3$.

After the vigorous reaction between the oxime (11 g.) and warm Ac_2O (20 c.c.) had subsided, the mixture was heated on the steam-bath for 10 min. and poured into H_2O (150 c.c.). 24 Hr. later 2-hydroxyphenylacetonitrile mixed with oily impurities was collected, washed, and dissolved in 3% aq. NaOH. After the addition of charcoal the solution was filtered, and on acidification with AcOH gave the nitrile as a colourless solid, which separated from C_6H_6 in short rhombic prisms, m. p. 122° (Found: N, 10·7. Calc. for C_8H_7ON: N, 10·5%) (Auwers, *Ber.*, 1907, **40**, 3513, gives m. p. 117—119°). Addition of $FeCl_3$ to an aq. solution of the compound gives a pale violet coloration; an alc. solution does not give a coloration.

Azlactones of Diacetylresorcylaldehyde and of 2-*Acetyl*-4-O-*methylresorcylaldehyde*.—Simultaneous acetylation and condensation of resorcylaldehyde with hippuric acid by means of Ac_2O and AcONa gave rise to the *azlactone* of the aldehyde diacetate, which crystallised from EtOH in buff-coloured needles, m. p. 130° (Found: C, 65·5; H, 4·3. $C_{20}H_{15}O_6N$ requires C, 65·8; H, 4·1%).

Similarly 4-*O*-methylresorcylaldehyde formed the *azlactone* of the acetate, which separated from EtOH in straw-coloured, elongated, hexagonal prisms, m. p. 150° (Found: C, 67·4; H, 4·8. $C_{19}H_{15}O_5N$ requires C, 67·7; H, 4·5%).

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