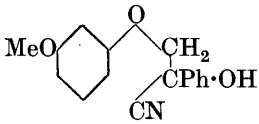
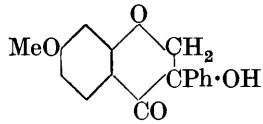
CLXXXIX.—*Synthetical Experiments in the* iso*Flavone Group. Part V. A New General Method applicable to the Synthesis of Derivatives of 7-Hydroxy-*iso*flavone.*

By Wilson Baker, Alfred Pollard, and Robert Robinson.

An extension of the experiments recorded in this series of memoirs to the synthesis of a wider range of *iso*flavones, including, for example, prunetin and irigenol, has become feasible as the result of the improved synthetic method now to be described, which is exemplified by the preparation of 7-methoxy*iso*flavone (VII).



(II.)



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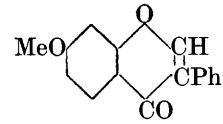
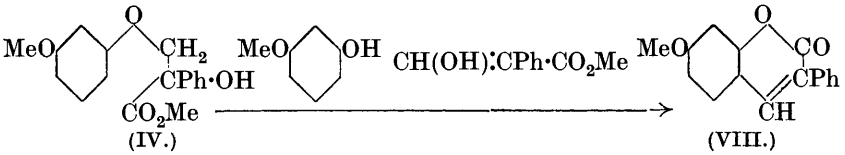


(VII.)

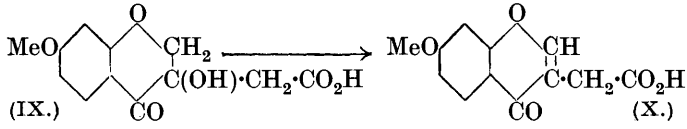
ω-m-*Methoxyphenoxyacetophenone* (resorcinol methyl phenacyl ether), $MeO{\cdot}C_6H_4{\cdot}O{\cdot}CH_2{\cdot}COPh$ (I), readily yielded a *cyanohydrin* (II), from which the related *hydroxy-acid*, $MeO{\cdot}C_6H_4{\cdot}O{\cdot}CH_2{\cdot}CPh(OH){\cdot}CO_2H$ (III) and its *methyl* ester (IV) and *amide* (V) were obtained. Numerous experiments on the dehydration of (III) did not result in the production of γ-pyrone derivatives, and the action of 80% sulphuric acid at 60° on (IV) gave a poor yield of a brightly fluor-

escent substance, m. p. 124°, identified as 7-methoxy-3-phenylcoumarin (VIII).

The formation of this substance suggests that the ester suffered hydrolytic fission, followed by recombination of the products in accordance with the scheme :



The nitrile (II) undergoes cyclisation to a *ketimine hydrochloride* when it is treated with zinc chloride and hydrogen chloride in ethereal solution. On hydrolysis, 3-*hydroxy*-7-*methoxy*isoflavanone (VI) is obtained, and this may be readily dehydrated by means of cold concentrated sulphuric acid. The last stage, in which the *iso*flavone (VII) is generated, recalls the transformation of brazilic acid (IX) into anhydrobrazilic acid (X) under the influence of sulphuric acid (Perkin, J., 1902, **81**, 221).



Anhydrobrazilic acid was synthesised in 1908 (Perkin and Robinson, J., **93**, 489), but, although the constitution of brazilic acid has thus been placed beyond doubt, the stereochemistry of the substance has not been investigated. The acid contains an original and unaffected asymmetric carbon atom of the brazilin skeleton, and it should be optically active; the relation of its configuration to that of glucose might be of interest in connexion with the phytochemical synthesis of brazilin from carbohydrates.

Obviously, it should be possible to effect the synthesis of brazilic acid by a simple application of the process which we have elaborated, but we shall not proceed to this in view of the appearance, when our work was almost completed, of a paper by Pfeiffer and Willems (*Ber.*, 1929, **62**, 1243) in which some of the necessary intermediates are described.

On the other hand, two of us, in collaboration with Professor W. H. Perkin, initiated, in October, 1928, a synthetical investigation in the brazilin and hæmatoxylin group on analogous lines, and it is proposed to continue this line of work.

In order to obtain an authentic specimen of 7-methoxy*iso*flavone, the original method described in Part I (J., 1925, **127**, 1981) has

been re-examined. The yield of *7-methoxyisoflavone-2-carboxylic acid* obtained by the oxidation of 7-methoxy-2-styryl*iso*flavone has been improved somewhat by modifying the conditions, and the opportunity has been taken to supplement the account given in Part I by the analysis and characterisation of this acid.

EXPERIMENTAL.

ω-m-*Methoxyphenoxyacetophenone* (I).—A solution of *m*-methoxyphenol (45 g.) in aqueous sodium hydroxide (10 g. in 50 c.c.) was added to one of phenacyl bromide (50 g.) in acetone (60 c.c.). The yellow liquid became orange and two layers separated. After gently heating on the steam-bath for 15 minutes, most of the acetone was removed by distillation and the residue mixed with cold water (500 c.c.). The precipitated oil rapidly crystallised, and the *substance* separated from alcohol in colourless needles (48 g., or 66%); after recrystallisation, these had m. p. 85—86° (Found : C, 74·2; H, 5·9. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%).

This ether is readily soluble in most organic solvents, but it is sparingly soluble in light petroleum. It dissolves in sulphuric acid at — 5° to an orange solution with evolution of heat; the solution exhibits a green fluorescence, and this is bright greenish-yellow in ultra-violet light. Addition of water to the orange solution precipitates a yellow oil which crystallises. This is, doubtless, crude 6-methoxy-3-phenylcoumarone; in ethereal solution it exhibits a bright blue fluorescence in ultra-violet light. It crystallises from a rather concentrated solution in light petroleum in colourless needles, m. p. 43°. If the temperature of the sulphuric acid solution is allowed to rise, an entirely different, more complex, substance is the sole product.

α-m-*Methoxyphenoxymethylmandelonitrile* (II).—A solution of ω-*m*-methoxyphenoxyacetophenone (25 g.) in ether (250 c.c.) was shaken with a solution of potassium cyanide (27·5 g. in 125 c.c. of water) while 30% sulphuric acid (50 c.c.) was added during 2 days. After shaking over-night, following the last addition of acid, the ethereal solution was separated, washed several times with water, and dried. Removal of the ether left a yellow oil, solidifying on keeping; when this was recrystallised from chloroform–light petroleum, the *cyanohydrin* was obtained in almost colourless prisms, m. p. 84—85·5° (yield, almost theoretical) (Found : C, 71·2; H, 5·8; N, 4·7. $C_{16}H_{15}O_3N$ requires C, 71·4; H, 5·6; N, 5·2%). The substance is very readily soluble in ether, acetone, chloroform, and benzene, but it is sparingly soluble in petroleum. On boiling with aqueous alcohol, the original ketone is re-formed with loss of hydrocyanic acid.

α-m-*Methoxyphenoxymethylmandelic Acid* (III) *and its Amide* (V) *and Methyl Ester* (IV).—A solution of the cyanohydrin (12 g.) in dry ether (30 c.c.) and methyl alcohol (3 c.c.) was saturated with dry hydrogen chloride at 0°. After remaining in the refrigerator for 3 days, the solution was added to crushed ice, and then heated in the steam-bath for ½ hour. The oil was taken up and washed in ether, recovered, and heated under reflux with alcohol (30 c.c.) and potassium hydroxide (5 g. in a few c.c. of water) for an hour. After dilution with several times its volume of water, the solution was saturated with carbon dioxide. A crystalline precipitate (3·1 g.) gradually separated from the turbid liquid. This *amide* crystallised from ethyl alcohol in needles, m. p. 122—123° (Found : C, 67·0; H, 6·1; N, 5·0. $C_{16}H_{17}O_4N$ requires C, 67·0; H, 5·9; N, 4·9%).

The clear aqueous solution, after being extracted with ether several times, was acidified with hydrochloric acid and extracted with chloroform. The chloroform solution, on evaporation, gave 7 g. of a white crystalline *acid*, m. p. 96—97°; this fell, on crystallisation from chloroform or alcohol, to 74—76° (Found : C, 63·3; H, 6·0. $C_{16}H_{16}O_5,H_2O$ requires C, 62·7; H, 5·9%), but the hard crystals that separated from chloroform–light petroleum had m. p. 95—97°. On keeping, the melting point of the lower-melting form was raised to 95—97°. Evidently, the substance forms a very unstable hydrate (Found in material dried in a vacuum over phosphoric oxide : C, 66·8; H, 5·7. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%). This acid dissolves in sulphuric acid to a solution which has the fluorescence characteristic of ω-*m*-methoxyphenoxyacetophenone under similar conditions.

A solution of the acid (5 g.) in dry ether (30 c.c.) was gradually added to a solution of diazomethane in ether (from 4 c.c. of nitrosomethylurethane). Evolution of nitrogen immediately occurred and, after ¼ hour, a stream of dry air was passed through the pale yellow liquid. After the evaporation of the ether, the yellow syrupy residue solidified to a mass of rhombic crystals, colourless after being washed with a little ether–petroleum, and having m. p. 48—49° (Found : C, 67·8; H, 6·0. $C_{17}H_{18}O_5$ requires C, 67·6; H, 6·0%).

This *methyl* α-m-*methoxyphenoxymethylmandelate* (1 g.), mixed with sulphuric acid (5 c.c. of 80%), was heated to 60° during ¼ hour, and the liquid maintained at that temperature for ½ hour. The red solution, which had a bright bluish-violet fluorescence, was added to crushed ice and the whole was extracted with ether. After removal of the solvent, the residue was heated for a short time with methyl-alcoholic potassium hydroxide. After acidification by means of hydrochloric acid, the solution was heated on

the steam-bath for ½ hour, cooled, and extracted with ether. The substance thus isolated crystallised from alcohol (charcoal) in colourless leaflets, m. p. 124°. The bright bluish-violet fluorescence of the neutral solutions of this substance and its behaviour as a lactone suggested that it might be 7-methoxy-3-phenylcoumarin (Bargellini, *Gazzetta*, 1927, **57**, 459; Baker, J., 1927, 2898), which has m. p. 124°. A mixture of an authentic specimen of the phenylmethoxycoumarin and of the substance obtained as described above had m. p. 124°.

3-*Hydroxy*-7-*methoxy*isoflavanone (VI).—Powdered anhydrous zinc chloride (1 g.) was added to a solution of α-*m*-methoxyphenoxymethylmandelonitrile (4 g.) in anhydrous ether (20 c.c.), and the whole saturated with hydrogen chloride for several hours and kept in the refrigerator for 3—4 days. The ether was then decanted, the greenish residue washed with fresh ether, ice added, and the mixture heated on the steam-bath and finally boiled; the product, isolated by means of ether, crystallised from alcohol in well-shaped, compact, colourless prisms, m. p. 133—135° (Found: C, 71·2; H, 5·5. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%).

This substance is moderately readily soluble in most organic solvents. It is reduced by means of sodium amalgam in methyl-alcoholic solution, with formation of a crystalline substance* which dissolves in sulphuric acid to a yellow solution exhibiting an intense green fluorescence. The reduction product is, doubtless, the corresponding secondary alcohol, and the action of sulphuric acid produces a solution of 7-methoxy*iso*flavylium sulphate. The highly characteristic fluorescence is not destroyed on dilution with alcohol or acetic acid: this is a recognised property of the 7-methoxybenzopyrylium salts.

Oxidation of 7-*Methoxy*-2-*styryl*isoflavone.—A solution of potassium permanganate (5 g.) in water (200 c.c.) at 25° was added in four portions to a solution of 7-methoxy-2-styryl*iso*flavone (4 g.) in pyridine (200 c.c.) at 25°, the temperature being kept below 40°. When all the permanganate was reduced (about 10 minutes), the solution was filtered, and distilled under diminished pressure until a cloudiness appeared. Excess of dilute hydrochloric acid was now added and, while still warm, the solution was extracted with a large volume of ethyl acetate. The ethyl acetate layer was separated, washed with water, and shaken with excess of aqueous sodium carbonate. The alkaline solution was acidified, the precipitated acids were collected, washed, and dried, and the benzoic

* (Added in proof.)—This 3:4-*dihydroxy*-7-*methoxy*isoflavane separates from benzene in colourless, glistening, elongated, pointed plates, m. p. 153° (Found: C, 70·5; H, 6·0. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9 %).

acid was removed by extraction with a little ether, leaving an almost white, crystalline powder (0·55 g.). This carboxylic acid crystallised readily from acetic acid, in which it was somewhat sparingly soluble, in colourless, diamond-shaped crystals, m. p. 241° with immediate loss of carbon dioxide (Found : C, 68·8; H, 4·1. $C_{17}H_{12}O_5$ requires C, 68·9; H, 4·1%). *7-Methoxyisoflavone-2-carboxylic acid* dissolves in concentrated sulphuric acid to a pale yellow solution which is devoid of fluorescence (magnesium light).

7-Methoxyisoflavone.—(A) The 7-methoxy*iso*flavone-2-carboxylic acid was heated at 250° until evolution of carbon dioxide had ceased (about 5 minutes). The melt, which solidified on cooling, crystallised from methyl alcohol (charcoal) in thin, glistening, colourless, six-sided plates, m. p. 156°. 7-Methoxy*iso*flavone dissolves in concentrated sulphuric acid to a colourless solution, the blue fluorescence of which is marked in sunlight and is brilliant in ultra-violet light.

(B) 3-Hydroxy-7-methoxy*iso*flavanone (0·1 g.) was dissolved in cold concentrated sulphuric acid (2 c.c.), and water added to the fluorescent solution after 30 minutes. The colourless precipitate was practically pure 7-methoxy*iso*flavone (yield, quantitative). The substance crystallised from ethyl alcohol in leaflets, m. p. 155°, and then from methyl alcohol in six-sided laminæ or flat, elongated, hexagonal prisms, m. p. 156°, unchanged by admixture with the substance obtained as in (A) (Found : C, 75·9; H, 4·9. Calc. for $C_{16}H_{12}O_3$: C, 76·1; H, 4·8%). The identity of the specimens was confirmed by a direct comparison of their properties.

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