CCCCVIII.—*Synthetical Experiments in the* iso*Flavone Group. Part III. A Synthesis of Genistein.*

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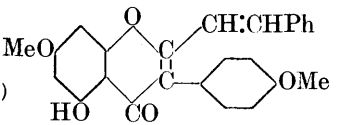
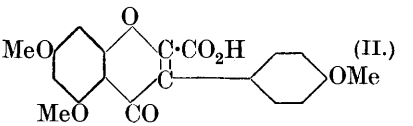
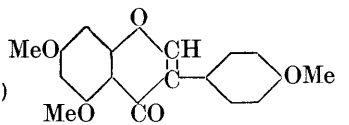
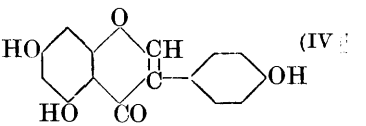
THE synthesis of methylgenistein dimethyl ether described in Part II of this investigation (J., 1926, 2713) sufficed to determine the constitution of genistein (prunetol), and we are now able to report the synthesis of the colouring matter itself by an extension of the methods previously employed.

When 5 : 7-dihydroxy-4′-methoxy-2-styryl*iso*flavone (Baker and Robinson, *loc. cit.*) was methylated by means of methyl sulphate and methyl-alcoholic aqueous potassium hydroxide, nuclear alkylation was avoided and the product was 5-*hydroxy*-7 : 4′-*dimethoxy*-2-*styryl*iso*flavone* (I), which was quite insoluble in boiling aqueous potassium hydroxide and could not be further methylated by means of methyl sulphate and potassium hydroxide in boiling methyl-alcoholic solution.

(I.) 



(III.) 



In the presence of acetone, however, the action of methyl sulphate and sodium hydroxide on the phenol led to the formation of

5 : 7 : 4′-*trimethoxy*-2-*styryl*iso*flavone*. We wish to direct particular attention to this modification of the usual procedure, since we have found in other cases that it is remarkably effective.

Several attempts to prepare derivatives of genisteincarboxylic acid by oxidation of the acetyl derivative of (I) were unsuccessful, but the methyl ether could be oxidised by means of potassium permanganate in aqueous pyridine solution with formation of benzoic acid and 5 : 7 : 4′-*trimethoxy*iso*flavone*-2-*carboxylic acid* (II). This acid decomposes smoothly, when heated above its melting point, yielding 5 : 7 : 4′-*trimethoxy*iso*flavone* (III) or genistein trimethyl ether. The latter has not yet been obtained from genistein, but on demethylation it furnished 5 : 7 : 4′-trihydroxy*iso*flavone (IV), identical in all respects with genistein from *Genista tinctoria*, Linn. (Perkin and Newbury, J., 1899, **75**, 830), a specimen of which was very kindly sent to us by Professor A. G. Perkin.

EXPERIMENTAL.

5-*Hydroxy*-7 : 4′-*dimethoxy*-2-*styryl*iso*flavone* (I).—Methyl sulphate and aqueous potassium hydroxide (40%) were added in small portions alternately and with shaking to a solution of 5 : 7-dihydroxy-4′-methoxy-2-styryl*iso*flavone (Part II, *loc. cit.*) (7·5 g.) in methyl alcohol (100 c.c. of 50%) and potassium hydroxide (10 g.). The deep orange-yellow colour of the solution faded. The precipitated methylated product, after being washed successively with dilute aqueous potassium hydroxide, water, and alcohol, crystallised from much alcohol in tiny, bright yellow needles, m. p. 245—246° (Found: C, 74·8; H, 5·2. $C_{25}H_{20}O_5$ requires C, 75·0; H, 5·0%). The phenolic function is feebly exercised, since, although the alcoholic solution becomes greenish-brown on the addition of ferric chloride, the substance is insoluble in dilute caustic alkali solution. The solution in sulphuric acid is intensely yellow and exhibits a weak green fluorescence.

The *acetyl* derivative was prepared in the usual manner by means of acetic anhydride. It crystallised from alcohol in thin, yellow prisms, m. p. 203—204° (Found: C, 73·1; H, 5·2. $C_{27}H_{22}O_6$ requires C, 73·3; H, 5·0%). Hydrolysis regenerated 5-hydroxy-7 : 4′-dimethoxy-2-styryl*iso*flavone, m. p. 245—246°. Attempts to oxidise this derivative to *O*-dimethylgenisteincarboxylic acid by means of potassium permanganate in acetone at − 10° to − 15° and in pyridine were fruitless.

5 : 7 : 4′-*Trimethoxy*-2-*styryl*iso*flavone* (Methyl ether of I).—Methyl sulphate (100 c.c.) and aqueous sodium hydroxide (100 c.c. of 20%) were added to a solution of 5-hydroxy-7 : 4′-dimethoxy-2-styryl*iso*flavone (10 g.) in acetone (400 c.c.). The mixture was

not cooled and the acetone layer, at first orange, became lemon-yellow; thereupon aqueous sodium hydroxide (50 c.c. of 20%) and methyl sulphate (50 c.c.) were added. Subsequently the liquid was kept strongly alkaline by the further gradual addition of 20% sodium hydroxide (100 c.c.). The product, obtained in theoretical yield, was precipitated by water (500 c.c.) and collected. It gave no coloration with ferric chloride in alcoholic solution and crystallised from alcohol in pale yellow, iridescent needles, m. p. 193° (Found: C, 75·3; H, 5·3. $C_{26}H_{22}O_5$ requires C, 75·4; H, 5·3%). The crystals are plank-shaped with obliquely cut ends and give an intensely yellow solution in sulphuric acid.

5 : 7 : 4′-*Trimethoxy*-2-*styryl*-6(?)-*methyl*iso*flavone*, prepared in a like manner from 5-hydroxy-7 : 4′-dimethoxy-2-styrylmethyl*iso*-flavone (Part II, *loc. cit.*), crystallised from alcohol in pale yellow needles, m. p. 211° with some previous shrinking (Found: C, 75·9; H, 5·7. $C_{27}H_{24}O_5$ requires C, 75·7; H, 5·6%). A mixture of this nuclear methylated compound with its lower homologue (m. p. 193°) melted at 175—180°.

5 : 7 : 4′-*Trimethoxy*iso*flavone*-2-*carboxylic Acid* (II).—A solution of potassium permanganate (15 g.) in water (500 c.c.) at about 30° was rather quickly added to one of 5 : 7 : 4′-trimethoxy-2-styryl*iso*-flavone (9 g.) in pure pyridine (500 c.c.) at about 35°. The oxidation was accompanied by a considerable rise of temperature. When the permanganate was reduced, the solution was filtered and distilled under about 100 mm. pressure until the liquid clouded and frothed excessively. The mixture was at once rendered strongly acid and while still warm the precipitated sticky orange mass was taken up in ethyl acetate. The extract was washed with water and then with aqueous sodium carbonate; the latter washings gave an ochreous precipitate on acidification. This was collected and heated with a little acetic acid in order to dissolve the impurities; the colourless, sandy residue (0·78 g.) was practically pure *trimethoxy*iso*flavone-carboxylic acid*. This derivative crystallises from acetic acid, in which it is very sparingly soluble, in satiny, microscopic, well-formed prisms, m. p. 237° (sharp but with immediate rapid decomposition) (Found: C, 63·8; H, 4·7. $C_{19}H_{16}O_7$ requires C, 64·0; H, 4·5%).

5 : 7 : 4′-*Trimethoxy*iso*flavone* (III).—The foregoing carboxylic acid was carefully heated above its melting point; the product crystallised several times from methyl alcohol in colourless, glistening, prismatic needles, m. p. 162—163° (Found: C, 69·1; H, 5·4. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·2%). It also separated under some undetermined conditions in rhombic plates, m. p. 162—163°.

5 : 7 : 4′-*Trihydroxy*iso*flavone* (Genistein, Prunetol, IV).—For the demethylation, the trimethyl ether was recovered from the methyl-

alcoholic mother-liquor, 0·52 g., m. p. 159—161°, being obtained. This was dissolved in a boiling mixture of acetic acid (10 c.c.) and acetic anhydride (5 c.c.), and colourless hydriodic acid (25 c.c., *d* 1·7) gradually introduced. After 20 minutes' boiling, two-thirds of the liquid was removed by distillation and water and sulphurous acid were added. The product was collected and acetylated by boiling for 30 minutes with acetic anhydride and a drop of pyridine. The acetyl derivative was isolated, crystallised once (m. p. 195—198°) from methyl alcohol, and then hydrolysed by boiling dilute aqueous sodium hydroxide and a few drops of alcohol. The recovered phenol crystallised from aqueous alcohol in long, colourless needles, m. p. 290—291° after softening and reddening at about 284°. A mixture with natural genistein and the latter alone exhibited an identical behaviour.

The synthetical specimen showed all the reactions of genistein as described in Part II (*loc. cit.*), and finally the characteristic dimethyl ether, m. p. 140—142°, was prepared and directly compared (mixed m. p.) with a specimen of natural origin (actually from prunetin), but no divergences of properties were noticed.

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