381. *A New Synthesis of* iso*Flavones. Part I.*

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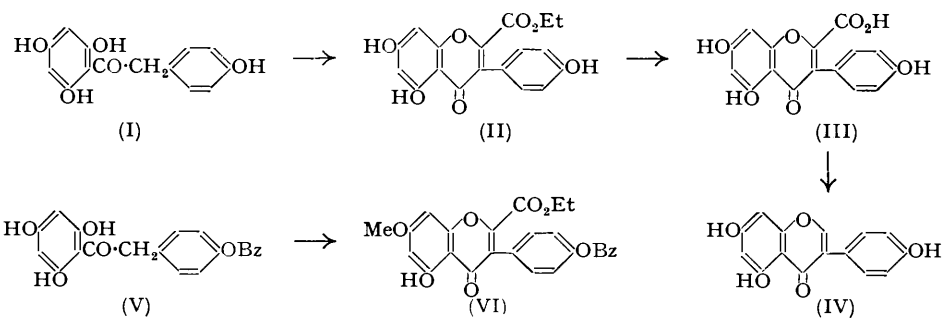
Benzyl *o*-hydroxyphenyl ketones (*e.g.*, I) react at room temperature with ethoxalyl chloride in pyridine to give 2-carbethoxy*iso*flavones (*e.g.*, II) in high yield. Hydrolysis to the carboxylic acids and thermal decarboxylation gives the *iso*flavones (*e.g.*, IV). Unlike the usual ethyl formate–sodium method which can only be satisfactorily used with mono- and di-hydroxylated benzyl phenyl ketones, the new synthesis is satisfactory with the tri- and poly-hydroxylated derivatives, and is particularly suited for the preparation of polyhydroxy- and partly alkoxylated *iso*flavones. Twelve *iso*flavones, six of them naturally occurring, have been synthesised, and the method may be used on a fairly large scale.

The ethoxalylation reaction involves direct *C*-ethoxalylation of the reactive methylene group, and cyclisation to 2-carbethoxy-2-hydroxy*iso*flavanones which have been isolated in some cases.

THE more important methods for the synthesis of *iso*flavones were briefly reviewed in a preliminary communication (Baker, Ollis, *et al.*, *Nature*, 1952, **169**, 706) in which the new process was outlined. The best previous method involved the formylation of benzyl *o*-hydroxyphenyl ketones by ethyl formate and sodium, a method which was first used for preparing chromones unsubstituted in position 2 by Perkin and Robinson in the case of anhydrobrazilic acid (*J.*, 1908, **93**, 504). In early applications (Späth and Lederer, *Ber.*, 1930, **63**, 743; Wesseley, Kornfeld, and Lechner, *Ber.*, 1933, **66**, 685) elevated temperatures were used and the yields of *iso*flavones were poor, but at or below room temperature, improved yields are obtained (Venkataraman, *J.*, 1934, 513, 1120, 1769), and this modification



has been widely used. It proceeds best when all hydroxyl groups in the benzyl phenyl ketone except that involved in cyclisation are protected, and fails when three or more free hydroxyl groups are present (see Baker *et al.*, *loc. cit.*).

The new *iso*flavone synthesis also starts from a benzyl *o*-hydroxyphenyl ketone (*e.g.*, I), but, unlike the ethyl formate process, proceeds equally well (in yields usually between 50 and 80%) when three or even more hydroxyl groups are present. It is particularly suited for the direct preparation of polyhydroxy- and partially alkoxylated hydroxy*iso*flavones. Dealkylation, which is here avoided, is sometimes accompanied by reorientation of a substituent group from position 8 to position 6 in 5-hydroxyflavones, and has been observed in these laboratories also in the *iso*flavone series (R. Winter, Dissertation, Bristol, 1950; I. Dunstan, unpublished observations; see also Baker, Dunstan, Harborne, Ollis, and Winter, *Chem. and Ind.*, 1953, 277; Whalley, *ibid.*, p. 277).

The benzyl *o*-hydroxyphenyl ketone (*e.g.*, I), containing in all *n* free phenolic hydroxyl groups, is treated with $(n + 1)$ equivalents of ethoxalyl chloride, $COCl{\cdot}CO_2Et$, in pyridine at room temperature, and left overnight. Addition of water then gives directly the 2-carbethoxy*iso*flavone (II), from which the related 2-carboxy*iso*flavone (III) is prepared by mild alkaline hydrolysis. The acid (III) is then converted into the *iso*flavone (IV) by decarboxylation at its melting point, a process which is best carried out rapidly with small quantities of acid.

The general applicability of the new method is illustrated by the synthesis of the following *iso*flavones, of which six occur naturally: 7-hydroxy-, 7-hydroxy-3′ : 4′-methylenedioxy- (ψ-baptigenin), 7 : 4′-dihydroxy- (daidzein), 4′-hydroxy-7-methoxy- (formononetin), 5 : 7-dihydroxy-, 5 : 7-dihydroxy-3′ : 4′-methylenedioxy-, 5 : 7 : 4′-trihydroxy- (genistein), 5 : 7-dihydroxy-4′-methoxy- (biochanin-A), 5 : 4′-dihydroxy-7-methoxy- (prunetin), 7 : 4′-dihydroxy-5-methoxy-, 7-hydroxy-4′-nitro-, and 5 : 7-dihydroxy-4′-nitro-*iso*flavone.

The synthesis of prunetin (genistein 7-methyl ether) by the new method involved protection of a phenolic group by benzoylation during and after a Hoesch reaction. Phloroglucinol and *p*-benzoyloxybenzyl cyanide gave 4-benzoyloxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone (V), converted by reaction with ethoxalyl chloride in pyridine into 4′-benzoyloxy-2-carbethoxy-5 : 7-dihydroxy*iso*flavone, and thence by partial methylation into 4′-benzoyloxy-2-carbethoxy-5-hydroxy-7-methoxy*iso*flavone (VI). Hydrolysis and decarboxylation then yielded prunetin (5 : 4′-dihydroxy-7-methoxy*iso*flavone).

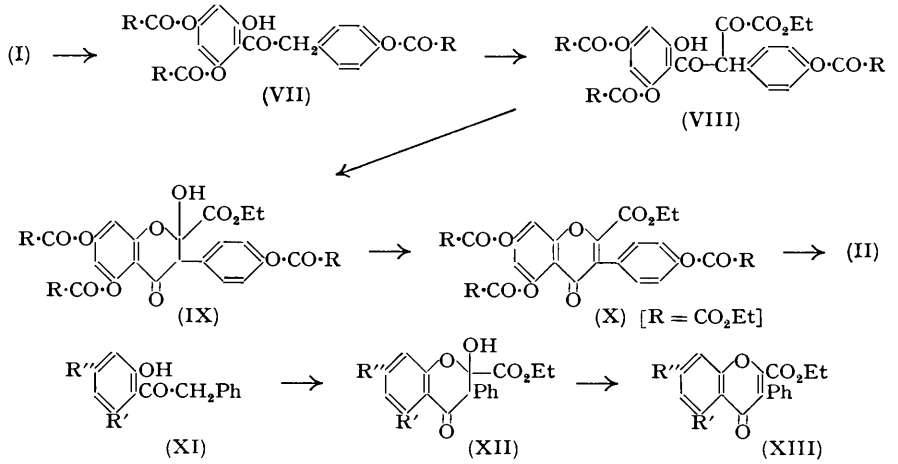
The isomeric 7 : 4′-dihydroxy-5-methoxy*iso*flavone (genistein 5-methyl ether), previously prepared from genistein by dibenzylation followed by methylation and debenzylation (Narasimhachari, Seshadri, and Sethuraman, *J. Sci. Ind. Res. India*, 1951, **10**, *B*, 195; King and Jurd, *J.*, 1952, 3211), has been more directly prepared from *p*-hydroxybenzyl cyanide and phloroglucinol monomethyl ether by the Hoesch reaction. The resulting 2 : 4-dihydroxy-6-methoxyphenyl 4-hydroxybenzyl ketone was then converted into 7 : 4′-dihydroxy-5-methoxy*iso*flavone by the new method [for orientation of ketones prepared by the Hoesch synthesis from phloroglucinol monomethyl ether, see *Org. Reactions*, 1949, **5**, 408, but in this reference for " 2 : 6-Dihydroxy-4-methoxybenzophenone " read " 2 : 4-Dihydroxy-6-methoxybenzophenone " (Karrer, *Helv. Chim. Acta*, 1919, **2**, 486); other cases not given in *Org. Reactions* are recorded by Sonn and Bülow, *Ber.*, 1925, **58**, 1691, and by Tamura, *Bull. Chem. Soc. Japan*, 1936, **11**, 781]. The ultra-violet absorption spectra of the three monomethyl ethers of genistein are recorded in the Experimental section. In the case of the 5-methyl ether there is a marked shift of the bands towards the shorter wave-lengths.

The usefulness of the new method for larger-scale preparations has been demonstrated by Mr. W. Lawson, of the Courtauld Institute of Biochemistry, Middlesex Hospital, who has synthesised 120 g. of genistein from 2 : 4 : 6-trihydroxyphenyl *p*-methoxybenzyl ketone in a yield of *ca.* 50% (personal communication). The intermediate yields were: ethoxalylation, 50—66%; hydrolysis, almost quantitative; decarboxylation (in portions of 6—8 g., at 300° for 8 min.), demethylation (boiled for 4 hr. with equal volumes of acetic acid and aqueous hydrobromic acid, *d* 1·48), and crystallisation from dilute ethanol, 75%.

Mechanism of the Ethoxalylation Reaction.—Although the conversion of, *e.g.*, *p*-hydroxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone (I) into 2-carbethoxy-5 : 7 : 4′-trihydroxy*iso*flavone (II) by reaction with ethoxalyl chloride and pyridine is in practice a single operation, it must involve a number of stages. In the general case these are probably: (1) ethoxalylation of all phenolic hydroxyl groups except one *ortho* to the carbonyl group, giving the

triethoxalyl derivative (VII); (2) direct *C*-ethoxalylation of the reactive methylene group to give (VIII); (3) cyclisation to the 2-carbethoxy-2-hydroxy*iso*flavanone (IX); (4) loss of a molecule of water to give the 2-carbethoxy*iso*flavone (X); (5) removal of the ethoxalyl groups by reaction with dilute acid, giving (II).

The following considerations support and amplify this reaction scheme. (*a*) The fact that it is necessary, in order to obtain the best yields, to employ $(n + 1)$ equivalents of ethoxalyl chloride in the case of a benzyl phenyl ketone containing n phenolic groups, indicates that the first step is the ethoxalylation of all phenolic groups except one in the *ortho* position to the carbonyl group. Phenols are rapidly ethoxalylated under the conditions employed, but a single hydroxyl group *ortho* to a carbonyl group is less readily attacked owing to hydrogen bonding; this is well known both for acylation and for alkylation. (*b*) The *C*-ethoxalylation is regarded as a direct process, rather than acylation of the last hydroxyl group followed by cyclisation to (IX) and dehydration to (X). This alternative is unlikely to occur under the conditions of the reaction. Partial ethoxalylation of the last hydroxyl group probably occurs simultaneously, and, whether or not *C*-ethoxalylation takes place afterwards, this represents a side reaction which does not lead to the 2-carbethoxy*iso*flavone. Preliminary experiments have shown that direct *C*-ethoxalylation of benzyl phenyl ketones occurs with ethoxalyl chloride in pyridine at room temperature, and the resulting 1 : 3-diketones yield co-ordinated copper derivatives. Ethoxalyl chloride, probably in the form of the acyl pyridinium salt, $C_5H_5N{\cdot}CO{\cdot}CO_2Et\}Cl$, reacts differently from simple acid chlorides; *e.g.*, benzyl 2-hydroxy-4 : 6-dimethoxypheny ketone reacts with benzoyl chloride in pyridine to give the *O*-benzoyl derivative (Ollis and Weight, *J.*, 1952, 3826), but the same ketone with ethoxalyl chloride in pyridine gives 2-carbethoxy-5 : 7-dimethoxy*iso*flavone (this paper). (*c*) 2-Carbethoxy-2-hydroxy*iso*flav-



anones have been isolated in several cases. Thus, benzyl *o*-hydroxyphenyl ketone (XI; R′ = R″ = H) and benzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone (XI; R′ = R″ = OMe) with ethoxalyl chloride under the usual conditions give the non-phenolic 2-carbethoxy-2-hydroxy*iso*flavanones (XII; R′ = R″ = H, and R′ = R″ = OMe respectively). A similar intermediate (XII; R′ = H, R″ = OMe) is also probably formed from benzyl 2-hydroxy-4-methoxyphenyl ketone (XI; R′ = H, R″ = OMe), though in this case it could not be obtained solid and may be a mixture of stereoisomerides. (*d*) These 2-hydroxy*iso*flavanones (XII) are β-hydroxy-carbonyl compounds and readily lose water, *e.g.*, on treatment with hydrochloric acid in acetic acid, to give the 2-carbethoxy*iso*flavones (XIII). With (XII; R′ = R″ = OMe) dehydration is also brought about by potassium hydroxide in pyridine, and simultaneous hydrolysis of the ester group gives the related 2-carboxy*iso*flavone. In many cases of the new synthesis the strongly electron-attracting ethoxalyloxy-groups in positions 5 and 7 of the intermediate 2-hydroxy*iso*flavanones

(as IX) facilitate ionisation of the proton from $C_{(3)}$, in consequence of which spontaneous dehydration occurs with formation of the 2-carbethoxy*iso*flavone (X). It is possible that this elimination of water may occur indirectly *via* an intermediate 2-ethoxalyloxy-derivative; loss of the very stable ethoxalyloxy-ion is likely to occur more readily than loss of the hydroxyl ion (see Southwick and Seivard, *J. Amer. Chem. Soc.*, 1949, **71**, 2532). (*e*) Ethoxalyl derivatives of phenols are very readily hydrolysed so that pouring the reaction mixture into water, extraction with chloroform, and shaking with dilute hydrochloric acid gives the hydroxylated 2-carbethoxy*iso*flavone (II) or the hydroxylated 2-carbethoxy-2-hydroxy*iso*flavanone, *e.g.*, (XII; R′ = R″ = OH).

Further Observations on the Ethoxalylation Reaction.—Reaction of benzyl *o*-hydroxyphenyl ketones with ethoxalyl chloride and pyridine in boiling benzene gave 2-carbethoxy-*iso*flavones directly in most cases which normally yielded the 2-hydroxy*iso*flavanones, but the yields were very low. However, in the case of benzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone (XI; R′ = R″ = OMe) the product was the *O*-ethoxalyl derivative of (XII; R′ = R″ = OMe), whose structure was proved by hydrolysis with potassium hydroxide in pyridine to (XII; R′ = R″ = OMe), and by boiling with acetic anhydride and sodium acetate which gave the 2-carbethoxy*iso*flavone (XIII; R′ = R″ = OMe).

2-Hydroxy*iso*flavanones have been recognised as intermediates in the ethyl formate *iso*flavone synthesis (Wolfrom, Mahan, Morgan, and Johnson, *J. Amer. Chem. Soc.*, 1941, **63**, 1248, 1253), and we now find that in the case of benzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone (XI; R′ = R″ = OMe) the primary product of the reaction is 2-hydroxy-5 : 7-dimethoxy*iso*flavanone, which loses water when treated with acetic acid to give 5 : 7-dimethoxy*iso*flavone.

Experimental

Crystallisation was from ethanol, except as given in parentheses. Substances are colourless unless otherwise stated.

*Ethoxalylation of Benzyl 2-Hydroxyphenyl Ketones. 2-Carbethoxy*iso*flavones* (with P. J. L. Binns, I. Dunstan, and A. Rutt).—To an ice-cold solution of the benzyl 2-hydroxyphenyl ketone in pyridine (*ca.* 10 c.c. for 1 g. of ketone) was slowly added redistilled ethoxalyl chloride [$(n + 1)$ equivs. for a ketone containing n phenolic groups], with shaking. Next day the mixture was poured into water and extracted with chloroform, and the organic layer washed with 10% hydrochloric acid, dried ($MgSO_4$), and evaporated. The product was then crystallised, and, in some cases, dried over phosphoric anhydride to remove traces of pyridine. The following ten 2-carbethoxy*iso*flavones were prepared in this way.

Benzyl 2 : 4-dihydroxyphenyl ketone (Chapman and Stephen, *J.*, 1923, **123**, 404; Badcock, Cavill, Robertson, and Whalley, *J.*, 1950, 2963) gave *2-carbethoxy-7-hydroxy*iso*flavone* (31%), plates, m. p. 211·5° (Found: C, 70·3; H, 4·7; OEt, 15·7. $C_{16}H_9O_4{\cdot}OEt$ requires C, 69·7; H, 4·5; OEt, 14·5%) [*monoacetyl* derivative, m. p. 76—77° (Found: C, 67·9; H, 4·2. $C_{20}H_{16}O_6$ requires C, 68·2; H, 4·6%)].

2 : 4-Dihydroxyphenyl 3 : 4-methylenedioxybenzyl ketone (Späth and Schmidt, *Monatsh.*, 1929, **53**, 454) gave 2-carbethoxy-7-hydroxy-3′ : 4′-methylenedioxy*iso*flavone (75%), yellow needles, m. p. 253° (Found: C, 64·5; H, 4·2. $C_{19}H_{14}O_7$ requires C, 64·5; H, 4·0%) [*monoacetyl* derivative, m. p. 170° (Found: C, 63·4; H, 4·0. $C_{21}H_{16}O_8$ requires C, 63·6; H, 4·05%)].

2 : 4-Dihydroxyphenyl 4-methoxybenzyl ketone (Baker and Eastwood, *J.*, 1929, 2902) gave *2-carbethoxy-7-hydroxy-4′-methoxy*iso*flavone* (76%), m. p. 209—210° (Found: C, 66·6; H, 4·7. $C_{19}H_{16}O_6$ requires C, 67·0; H, 4·7%) [*monoacetyl* derivative, m. p. 123° (Found: C, 65·9; H, 4·8. $C_{21}H_{18}O_7$ requires C, 66·0; H, 4·7%)].

2 : 4-Dihydroxyphenyl 4-hydroxybenzyl ketone (Walz, *Annalen*, 1931, **489**, 118) gave *2-carbethoxy-7 : 4′-dihydroxy*iso*flavone* (50%) (from aqueous ethanol), m. p. 194—195° (Found: C, 62·7; H, 4·4. $C_{18}H_{14}O_6{,}H_2O$ requires C, 62·8; H, 4·7%) [*diacetyl* derivative, m. p. 145° (Found: C, 64·1; H, 4·5. $C_{22}H_{18}O_8$ requires C, 64·4; H, 4·4%)].

2 : 4-Dihydroxyphenyl 4-nitrobenzyl ketone (Joshi and Venkataraman, *J.*, 1934, 513) gave *2-carbethoxy-7-hydroxy-4′-nitro*iso*flavone* (40%), m. p. 229° (Found: C, 60·9; H, 3·6; N, 4·0. $C_{18}H_{13}O_7N$ requires C, 60·8; H, 3·7; N, 3·95%) [*monoacetyl* derivative, m. p. 143° (Found: C, 60·0; H, 3·9. $C_{20}H_{15}O_8N$ requires C, 60·5; H, 3·8%)].

3 : 4-*Methylenedioxybenzyl* 2 : 4 : 6-*trihydroxyphenyl ketone*, prepared by the Hoesch reaction

from phloroglucinol and 3 : 4-methylenedioxyphenylacetonitrile formed needles (65%), m. p. 202° (Found : C, 62·7; H, 4·2. $C_{15}H_{12}O_6$ requires C, 62·5; H, 4·2%). It gave *2-carbethoxy-5 : 7-dihydroxy-3' : 4'-methylenedioxyisoflavone* (87%), yellow needles (from aqueous ethanol), m. p. 223° (Found : C, 61·7; H, 3·7; OEt, 11·2. $C_{17}H_9O_7$·OEt requires C, 61·6; H, 3·8; OEt, 12·2%) [*diacetyl* derivative, m. p. 158—159° (Found : C, 60·6; H, 4·0. $C_{23}H_{18}O_{10}$ requires C, 60·8; H, 4·0%)].

Benzyl 2 : 4 : 6-trihydroxyphenyl ketone (Badcock *et al., loc. cit.*) gave *2-carbethoxy-5 : 7-dihydroxyisoflavone* (45%), light yellow needles, m. p. 230° (Found : C, 66·1; H, 4·2; OEt, 13·2. $C_{16}H_9O_5$·OEt requires C, 66·25; H, 4·3; OEt, 13·8%) [*diacetyl* derivative, m. p. 153—154° (Found : C, 64·5; H, 4·4. $C_{22}H_{18}O_8$ requires C, 64·4; H, 4·4%)].

4-Hydroxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone (I) (Baker and Robinson, *J.*, 1926, 2716) gave *2-carbethoxy-5 : 7 : 4'-trihydroxyisoflavone* (II) (55%), yellow prisms, m. p. 240—242° (decomp.) (Found : C, 63·0; H, 4·3; OEt, 13·3. $C_{16}H_9O_6$·OEt requires C, 63·15; H, 4·1; OEt, 13·2%) [*triacetyl* derivative, m. p. 181—183° (Found : C, 61·4; H, 4·4; OEt, 10·0. $C_{22}H_{15}O_9$·OEt requires C, 61·5; H, 4·3; OEt, 9·6%)].

4-Methoxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone (Badcock *et al., loc. cit.*) gave *2-carbethoxy-5 : 7-dihydroxy-4'-methoxyisoflavone* (60%), pale yellow needles (from benzene), m. p. 189—190° (Found : C, 64·4; H, 4·6. $C_{19}H_{16}O_7$ requires C, 64·0; H, 4·5%) [*diacetyl* derivative, m. p. 166—167° (Found : C, 62·6; H, 4·7. $C_{23}H_{20}O_9$ requires C, 62·7; H, 4·6%); *dimethyl ether*, m. p. 150—151° (Found : C, 65·6; H, 5·4. $C_{21}H_{20}O_7$ requires C, 65·6; H, 5·2%)].

4-Nitrobenzyl 2 : 4 : 6-trihydroxyphenyl ketone (Yamashita, *Chem. Abs.*, 1930, **24**, 2443) gave *2-carbethoxy-5 : 7-dihydroxy-4'-nitroisoflavone* (52%), yellow plates (from aqueous ethanol), m. p. 190—191° (Found : C, 58·5; H, 3·8. $C_{18}H_{13}O_8N$ requires C, 58·2; H, 3·5%) [*diacetyl* derivative, m. p. 210—211° (Found : C, 58·0; H, 3·7; N, 3·5. $C_{22}H_{17}O_{10}N$ requires C, 58·0; H, 3·7; N, 3·1%)].

Hydrolysis and Decarboxylation of 2-Carbethoxyisoflavones. Preparation of isoFlavones (with P. J. L. Binns, I. Dustan, and A. Rutt).—The preceding esters were hydrolysed by either of the following methods. (*a*) To a solution of the ester in acetone was added 2N-sodium hydroxide (one equiv. for each phenolic group and one for the ester) and then water until the solution became clear. After 24 hr. at room temperature, the acetone was removed, and the solution acidified. (*b*) The ester in acetone or ethanol was warmed for 3—4 hr. with excess of 5% aqueous sodium carbonate. The organic solvent was evaporated, and the cooled solution acidified to pH 4. In each case the solid acid was collected, washed with water, and dried. The *iso*flavone-2-carboxylic acids were obtained as colourless to bright yellow crystalline powders, occasionally containing water of crystallisation. In two cases, the 2-carboxylic acids were purified and analysed (see below), but were usually directly decarboxylated.

In earlier experiments (marked *) decarboxylation was effected by heating the acids *in vacuo* in a sublimation apparatus; the *iso*flavones sublimed. It is, however, better to heat the acids rapidly in portions (*ca.* 50 mg.) some 10° above the m. p.s until evolution of carbon dioxide ceases (2—5 min.). The crude melt was either crystallised from a suitable solvent and washed with aqueous sodium hydrogen carbonate (to remove unchanged acid), or purified through its acetyl derivative.

The following were thus obtained :

7-Hydroxyisoflavone-2-carboxylic acid (80%), needles (from aqueous ethanol), m. p. 247° (decomp.) (Found : C, 64·1; H, 4·2. $C_{16}H_{10}O_5,H_2O$ requires C, 64·0; H, 4·0%). 7-Hydroxy*iso*flavone (75%), prisms, m. p. 213° (Found : C, 75·2; H, 4·3. Calc. for $C_{15}H_{10}O_3$: C, 75·6; H, 4·2%) (Venkataraman, *J.*, 1934, 1120, gives m. p. 215°).

7-Hydroxy-3 : 4-methylenedioxy*iso*flavone-2-carboxylic acid (70%) m. p. 275°. 7-Hydroxy-3' : 4'-methylenedioxy*iso*flavone (*ψ*-baptigenin) (61%), yellow crystals (from aqueous ethanol), m. p. 292° (Found : C, 67·9; H, 3·7. Calc. for $C_{16}H_{10}O_5$: C, 68·1; H, 3·6%) [monoacetyl derivative, m. p. 165° (Found : C, 66·6; H, 3·7. Calc. for $C_{18}H_{12}O_6$: C, 66·7; H, 3·7%)]. Mahal, Rai, and Venkataraman (*J.*, 1934, 1769) give m. p. 292—293° for *ψ*-baptigenin, and 176° for the monoacetyl derivative.

7-Hydroxy-4'-methoxy*iso*flavone-2-carboxylic acid (98%), m. p. 238°. 7-Hydroxy-4'-methoxy*iso*flavone (formononetin) (91%), plates, m. p. 257° (Found : C, 71·3; H, 4·7. Calc. for $C_{16}H_{12}O_4$: C, 71·6; H, 4·5%) [monoacetyl derivative, m. p. 166° (Found : C, 69·3; H, 4·65. Calc. for $C_{18}H_{14}O_5$: C, 69·7; H, 4·5%)]. Venkataraman (*loc. cit.*) gives m. p. 257° for formononetin, and 170° for the monoacetyl derivative.

7 : 4'-Dihydroxy*iso*flavone-2-carboxylic acid, m. p. 290° (88%). 7 : 4'-Dihydroxy*iso*flavone (daidzein), needles, m. p. 320—328° (decomp.) (98%) (Found : C, 70·6; H, 4·0. Calc. for

$C_{15}H_{10}O_4$: C, 70·9; H, 3·9%) [diacetyl derivative, m. p. 189° (Found: C, 67·8; H, 4·2. Calc. for $C_{19}H_{14}O_6$: C, 67·45; H, 4·1%)]. Venkataraman (*loc. cit.*) gives m. p. 310—322° (decomp.) for daidzein, and 184—187° for the diacetyl derivative.

7-Hydroxy-4′-nitro*iso*flavone-2-carboxylic acid, m. p. 252° (99%). 7-Hydroxy-4′-nitro*iso*flavone, needles, m. p. 292° (98%) (Found: C, 63·2; H, 3·1. $C_{15}H_9O_5N$ requires C, 63·6; H, 3·2%) [*monoacetyl* derivative, m. p. 222—223° (Found: C, 62·7; H, 3·15. $C_{17}H_{11}O_6N$ requires C, 62·8; H, 3·4%)].

5 : 7-Dihydroxy-3′ : 4′-methylenedioxy*iso*flavone-2-carboxylic acid, m. p. 264° (90%). 5 : 7-*Dihydroxy*-3′ : 4′-*methylenedioxy*iso*flavone*, pale yellow needles (from aqueous ethanol), m. p. 227° (8%*) (Found: C, 64·45; H, 4·4. $C_{16}H_{10}O_6$ requires C, 64·4; H, 3·4%) [*diacetyl* derivative, m. p. 216° (Found: C, 63·4; H, 4·4. $C_{20}H_{14}O_8$ requires C, 62·8; N, 3·7%)].

5 : 7-*Dihydroxy*iso*flavone-2-carboxylic acid*, yellow needles (from aqueous ethanol), m. p. 255° (decomp.) (76%) (Found: C, 62·1; H, 3·7. $C_{16}H_{10}O_6,\frac{1}{2}H_2O$ requires C, 62·5; H, 3·6%). 5 : 7-Dihydroxy*iso*flavone, plates, m. p. 195—196° (from benzene) (25%*) (Found: C, 71·0; H, 4·2. Calc. for $C_{15}H_{10}O_4$: C, 70·9; H, 3·9%) [*diacetyl* derivative, m. p. 173—174° (Found: C, 67·3; H, 4·0. $C_{19}H_{14}O_6$ requires C, 67·45; H, 4·1%)]. Iyer, Shah, and Venkataraman (*Current Sci.*, 1949, **18**, 404; *Proc. Indian Acad. Sci.*, 1951, **33**, *A*, 116) give m. p. 193—194° for 5 : 7-dihydroxy*iso*flavone.

5 : 7 : 4′-Trihydroxy*iso*flavone-2-carboxylic acid (III), m. p. 310° (84%). Acetylation of the crude decarboxylated material gave 5 : 7 : 4′-triacetoxy*iso*flavone (21%), m. p. 195—198° (Walter, *J. Amer. Chem. Soc.*, 1941, **63**, 3273, gives m. p. 200°), hydrolysis of which with aqueous-ethanolic sodium carbonate gave 5 : 7 : 4′-trihydroxy*iso*flavone (genistein) (IV), needles, m. p. 296° (decomp.) (88%) (Found: C, 66·2; H, 3·8. Calc. for $C_{15}H_{10}O_5$: C, 66·7; H, 3·7%). The pure compound gives a green colour with alcoholic ferric chloride. Walter (*loc. cit.*) gives the same m. p., but records a reddish-violet ferric chloride reaction with the natural product.

5 : 7-Dihydroxy-4′-methoxy*iso*flavone-2-carboxylic acid, m. p. 276° (98%). Acetylation of the crude, decarboxylated material gave the diacetyl derivative, needles, m. p. 189—190° (81%) (Found: C, 65·2; H, 4·3. Calc. for $C_{20}H_{16}O_7$: C, 65·2; H, 4·4%). Hydrolysis with aqueous-ethanolic sodium carbonate then gave 5 : 7-dihydroxy-4′-methoxy*iso*flavone (biochanin-A) (61%), needles (from aqueous ethanol), m. p. 211—212° (Found: C, 67·1; H, 4·0. Calc. for $C_{16}H_{12}O_5$: C, 67·6; H, 4·3%). Bose and Siddiqui (*J. Sci. Ind. Res. India*, 1945, **4**, 231) give m. p. 212° for biochanin-A, and 190° for the diacetyl derivative.

5 : 7-Dihydroxy-4′-nitro*iso*flavone-2-carboxylic acid, m. p. 260° (87%). 5 : 7-*Dihydroxy*-4′-*nitro*iso*flavone*, yellow needles, m. p. 294—295° (23%*) (Found: C, 60·4; H, 3·0; N, 4·8. $C_{15}H_9O_6N$ requires C, 60·2; H, 3·0; N, 4·7%) [*diacetyl* derivative, m. p. 212—213° (Found: C, 59·6; H, 3·2; N, 4·2. $C_{19}H_{13}O_8N$ requires C, 59·5; H, 3·4; N, 3·7%; dimethyl ether, m. p. 220—221° (Iyer, Shah, and Venkataraman, *locc. cit.*, give m. p. 220—222°)].

7 : 4′-*Dihydroxy*-5-*methoxy*iso*flavone*.—The Hoesch reaction between phloroglucinol monomethyl ether (7·6 g.; Robertson and Subramaniam, *J.*, 1937, 286) and *p*-hydroxybenzyl cyanide (7·3 g.) gave 2 : 4-*dihydroxy*-6-*methoxyphenyl* 4-*hydroxybenzyl ketone*, needles (from aqueous ethanol), m. p. 186—188° (8·5 g.) (Found: C, 65·3; H, 5·0; OMe, 10·5. $C_{14}H_{11}O_4$·OMe requires C, 65·7; H, 5·1; OMe, 11·3%). It gives a purple-red ferric chloride reaction. This ketone (2·4 g.) in pyridine (20 c.c.) was treated at 0° with ethoxalyl chloride (3·2 c.c.). After 18 hr. ice was added, and the oil extracted with chloroform (3 × 50 c.c.). When these extracts were washed with 10% aqueous hydrochloric acid, 2-*carbethoxy*-7 : 4′-*dihydroxy*-5-*methoxy*iso*flavone* separated at the interface. It forms cubes (from aqueous methanol), m. p. 223—224° (0·32 g., 10%) (Found, after drying at 160° for 5 hr.: C, 63·6; H, 4·5. $C_{19}H_{16}O_7$ requires C, 64·0; H, 4·5%). It gave no colour with ferric chloride. This ester was hydrolysed [the acid (83% yield) had m. p. 254—256°] and decarboxylated, giving 7 : 4′-dihydroxy-5-methoxy*iso*flavone (51%), needles (from aqueous ethanol), m. p. 316° (decomp.) (Found, after drying at 160° for 5 hr.: C, 67·7; H, 4·25. Calc. for $C_{16}H_{12}O_5$: C, 67·6; H, 4·3%). It gave no colour with aqueous-ethanolic ferric chloride. Its diacetyl derivative formed needles (from aqueous ethanol), m. p. 168—170° (88%) (Found: C, 64·8; H, 4·2. Calc. for $C_{20}H_{16}O_7$: C, 65·2; H, 4·4%). Narasimhachari, Seshadri, and Sethuraman (*J. Sci. Ind. Res. India*, 1951, **10**, *B*, 195) give m. p. 284—286° for this *iso*flavone; King and Jurd, *J.*, 1952, 3211, give m. p. 302° (decomp.), and 169·5° for the *iso*flavone and its diacetyl derivative.

5 : 4′-*Dihydroxy*-7-*methoxy*iso*flavone* (*Prunetin*).—*p*-Hydroxybenzyl cyanide (5·0 g.), pyridine (50 c.c.), and benzoyl chloride (5·36 c.c.) gave 4-*benzoyloxybenzyl cyanide* (7·5 g., 84%), needles, m. p. 106—108° (Found: C, 75·6; H, 4·8; N, 6·0. $C_{15}H_{11}O_2N$ requires C, 75·9; H, 4·6; N, 5·9%). The Hoesch reaction between 4-benzoyloxybenzyl cyanide (8·0 g.) and phloroglucinol

(10 g.) gave 4-*benzoyloxybenzyl* 2 : 4 : 6-*trihydroxyphenyl ketone* (V) which was washed with hot benzene (500 c.c.) and then crystallised from aqueous ethanol as needles (5·4 g., 44%), m. p. 224° (decomp.) (Found: C, 69·7; H, 4·6. $C_{21}H_{16}O_6$ requires C, 69·2; H, 4·4%). It gave a purple-brown colour with ferric chloride.

The ketone (3 g.) in pyridine (30 c.c.) was treated at 0° with ethoxalyl chloride (4 c.c.) and worked up in the usual way. The 4′-*benzoyloxy*-2-*carbethoxy*-5 : 7-*dihydroxy*iso*flavone* formed, yellow plates (from methanol) (2·48 g.), m. p. 248° (decomp.) (Found: C, 66·9; H, 3·8. $C_{25}H_{18}O_8$ requires C, 67·3; H, 4·0%). Its *diacetyl* derivative formed plates (from acetone), m. p. 232° (Found: C, 65·7; H, 4·2; OEt, 7·4. $C_{27}H_{17}O_9$·OEt requires C, 65·7; H, 4·2; OEt, 8·4%).

The ester (1·12 g.), benzene (150 c.c.), ignited potassium carbonate (5 g.), and methyl sulphate (0·27 c.c.) were kept at 100° for 2 hr. giving 4′-*benzoyloxy*-2-*carbethoxy*-5-*hydroxy*-7-*methoxy*iso*flavone* (VI) (0·92 g., 80%), pale yellow plates (from acetone), m. p. 202—204° (Found: C, 67·3; H, 4·1. $C_{26}H_{20}O_8$ requires C, 67·8; H, 4·4%). It gave an intense brown colour with ferric chloride. Hydrolysis gave 5 : 4′-dihydroxy-7-methoxy*iso*flavone-2-carboxylic acid (97%), m. p. 270°, and decarboxylation then gave 5 : 4′-dihydroxy-7-methoxy*iso*flavone (63%), needles (from methanol), m. p. 236° (Found: C, 67·7; H, 4·2; OMe, 11·4. Calc. for $C_{15}H_9O_4$·OMe: C, 67·6; H, 4·3; OMe, 10·9%) [diacetyl derivative, m. p. 218—220° (Found: C, 64·85; H, 4·5. Calc. for $C_{20}H_{16}O_7$: C, 65·2; H, 4·3%)]. King and Jurd (*loc. cit.*) give m. p.s 237—238° and 222·5° for natural prunetin and its diacetyl derivative.

*Reaction of Ethoxalyl Chloride with Benzyl o-Hydroxyphenyl Ketone. 2-Carbethoxy*iso*flavone.*—Ethoxalyl chloride (2·5 c.c.) was added with shaking to benzyl *o*-hydroxyphenyl ketone (2·11 g.; sublimed) in pyridine (20 c.c.). Next day the solution was poured into 10% acetic acid (100 c.c.), and the solid was collected, washed, and dried (3·02 g.), giving 2-*carbethoxy*-2-*hydroxy*iso*flavanone*, plates (from aqueous ethanol or benzene–light petroleum), m. p. 145° (2·59 g., 83%) (C, 68·8; H, 5·1; OEt, 12·8. $C_{16}H_{11}O_4$·OEt requires C, 69·2; H, 5·1; OEt, 14·4%). The 2 : 4-*dinitrophenylhydrazone*, yellow prisms (from acetic acid), m. p. 206° (decomp.) (Found: C, 58·4; H, 4·25; N, 11·4. $C_{24}H_{20}O_8N_4$ requires C, 58·5; H, 4·1; N, 11·4%). Dehydration of the 2-hydroxy*iso*flavanone by warm acetic and hydrochloric acids during ½ hr. gave 2-carbethoxy*iso*flavone (92%), rectangular plates, m. p. 96—97° (Found: C, 73·6; H, 4·9. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·8%).

iso*Flavone.*—2-*Carbethoxy*iso*flavone* (1·0 g.) and concentrated sulphuric acid (10 c.c.) were heated at 100° for ½ hr., then poured into water, and the product crystallised from chloroform–light petroleum (b. p. 60—80°). iso*Flavone*-2-*carboxylic acid* separated as needles (0·5 g., 73%), m. p. 212—213° (Found: C, 71·6; H, 4·3. $C_{16}H_{10}O_4$ requires C, 72·2; H, 3·8%). Unchanged ester (0·24 g.) was recovered from the mother-liquors.

The acid (0·38 g.) was heated for 15 min. at 220° (till gas evolution ceased), and the product was crystallised from aqueous ethanol, washed with dilute sodium hydrogen carbonate, and dried (0·22 g.; m. p. 128—130°). Crystallisation from light petroleum (b. p. 60—80°) raised the m. p. to 131°, undepressed when mixed with *iso*flavone (m. p. 131°) prepared by the formylation method (Joshi and Venkataraman, *J.*, 1934, 513). The formylation in our hands gave a crude yield of 82% of material, m. p. 126—128°, which, after crystallisation, had m. p. 131° (Joshi and Venkataraman obtained a 40% yield, and m. p. 132°).

Benzyl 2-Hydroxy-4-methoxyphenyl Ketone (with P. J. L. Binns and R. Winter).—This compound (see Tambor, *Ber.*, 1910, **43**, 1884; Badcock, Cavill, and Whalley, *J.*, 1950, 2963) is best prepared by Bentley and Robinson's method (*J.*, 1950, 1353), but, contrary to a statement in the literature, it can be readily made by the partial methylation of benzyl 2 : 4-dihydroxyphenyl ketone. This ketone (35 g.; m. p. 110—111°, crystallised from benzene), methyl sulphate (17·5 g.), potassium carbonate (100 g.), and benzene (200 c.c.) were boiled for 90 min., cooled, filtered, and evaporated, giving benzyl 2-hydroxy-4-methoxyphenyl ketone (18 g., 51%), needles, m. p. 88°.

Reaction of Ethoxalyl Chloride with Benzyl 2-Hydroxy-4-methoxyphenyl Ketone.—Ethoxalyl chloride (2 c.c.) was added to benzyl 2-hydroxy-4-methoxyphenyl ketone (2 g.) in pyridine (20 c.c.). Next day the solution was poured into water, extracted with chloroform (3 × 100 c.c.), washed with dilute hydrochloric acid (3 × 100 c.c.), dried, and evaporated, leaving an oil, possibly 2-carbethoxy-2-hydroxy-7-methoxy*iso*flavanone. This was warmed on a steam-bath (½ hr.) with acetic acid (20 c.c.) and concentrated hydrochloric acid (2 c.c.), then added to water, and the solid (2·01 g., 80%) crystallised from ethanol. 2-*Carbethoxy*-7-*methoxy*iso*flavone* formed prisms, m. p. 130—131° (Found: C, 70·5; H, 4·85. $C_{19}H_{16}O_5$ requires C, 70·4; H, 5·0%). It was also prepared (48%) by methylation of 2-carbethoxy-7-hydroxy*iso*-

flavone, and by reaction of benzyl 2-hydroxy-4-methoxyphenyl ketone with sodium and ethyl oxalate. The crude oil, after being heated with acetic acid and freed from acidic material, gave 2-carbethoxy-7-methoxy*iso*flavone (10%), m. p. and mixed m. p. 130—131° (Found : C, 70·6; H, 4·9%).

7-*Methoxy*iso*flavone* (with R. WINTER).—2-Carbethoxy-7-methoxy*iso*flavone (100 mg.) was dissolved in ethanol (5 c.c.), and 10% aqueous sodium hydroxide (0·14 c.c.) and water (5 c.c.) were added. After 7 hr. the mixture was acidified and diluted, and the solid (89 mg.; m. p. 242°, 97%) collected and crystallised (aqueous ethanol), giving 7-methoxy*iso*flavone-2-carboxylic acid as needles, m. p. 243° (decomp.), alone or when mixed with an authentic specimen (Baker, Pollard, and Robinson, *J.*, 1929, 1473). Decarboxylation at 250° for 10 min. gave 7-methoxyisoflavone (90%), plates (from methanol), m. p. and mixed m. p. 156° (Baker and Robinson, *J.*, 1925, 1986).

Reaction of Benzyl 2-Hydroxy-4 : 6-dimethoxyphenyl Ketone with Ethoxalyl Chloride.—(a) *At room temperature.* Ethoxalyl chloride (3 c.c.) was added with shaking to a solution of benzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone (5 g.) in pyridine (25 c.c.). After 18 hr., water was added, the whole was shaken with chloroform, and the extracts were washed with acid, dried, and evaporated. The 2-*carbethoxy*-2-*hydroxy*-5 : 7-*dimethoxy*iso*flavanone* crystallised from ethanol (35 c.c.) as prisms (4·7 g., 69%), m. p. 148—153° [Found : C, 64·7; H, 5·3; (OEt)(OMe)$_2$, 27·2. $C_{16}H_9O_4(OEt)(OMe)_2$ requires C, 64·6; H, 5·4; (OEt)(OMe)$_2$, 28·8%].

The preceding compound when heated with acetic and hydrochloric acids at 100° for 15 min. gave 2-*carbethoxy*-5 : 7-*dimethoxy*iso*flavone* (85%), m. p. and mixed m. p. with an authentic specimen (see below), 156—158°. When the above hydroxy-flavanone (1 g.) was shaken for 40 min. with potassium hydroxide (0·4 g.), the mixture poured into dilute acid, and the precipitate dissolved in aqueous sodium hydrogen carbonate, filtered and acidified, it gave 5 : 7-*dimethoxy*iso*flavone*-2-*carboxylic acid* (0·6 g., 68%), m. p. 224° (decomp.) (Found : C, 65·8; H, 4·4. $C_{18}H_{14}O_6$ requires C, 66·25; H, 4·3%).

(b) *In boiling benzene.* The ketone (4 g.), benzene (40 c.c.), pyridine (4 c.c.), and ethoxalyl chloride (3·25 c.c.) was kept at 100° for 2½ hr. and then filtered from pyridine hydrochloride, the solution was washed with dilute hydrochloric acid (3 × 25 c.c.), dried, and evaporated, and the oil crystallised from ethanol, giving 2-*carbethoxy*-2-*ethoxalyloxy*-5 : 7-*dimethoxy*iso*flavanone* (2 g., 30%), needles, m. p. 111—112° [Found : C, 60·3; H, 4·6; (OEt)(OMe), 31·6. $C_{18}H_8O_6(OEt)_2(OMe)_2$ requires C, 61·0; H, 5·1; (OEt)(OMe), 32·2%].

A solution of the preceding compound (0·5 g.) in pyridine (3·5 c.c.) and powdered potassium hydroxide (0·3 g.) was shaken for 20 min., and poured into water. The product was crystallised from water, giving 2-carbethoxy-2-hydroxy-5 : 7-dimethoxy*iso*flavanone (0·08 g., 20%), m. p. and mixed m. p. 152° with previous softening. Dehydration with glacial acetic acid gave 2-carbethoxy-5 : 7-dimethoxy*iso*flavone, a compound which was also formed when the above 2-ethoxalyloxy-derivative was heated for 4½ hr. with acetic anhydride and sodium acetate.

5 : 7-*Dimethoxy*iso*flavone* (with D. WEIGHT).—(*a*) A mixture of benzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone (3 g.), ethyl formate (40 c.c.), and powdered sodium (3 g.) was stirred at −10° for 2 hr., and kept at 0° for 48 hr. After addition of ice, the mixture yielded to ether a product (1·9 g.) which was crystallised from aqueous ethanol, giving 2-*hydroxy*-5 : 7-*dimethoxy*iso*flavanone*, prisms, m. p. 152° (Found : C, 68·0; H, 5·3. $C_{17}H_{16}O_5$ requires C, 68·05; H, 5·3%). This compound (0·5 g.), when warmed with glacial acetic acid (5 c.c.) for ½ hr. at 100°, gave 5 : 7-dimethoxy*iso*flavone, prisms, m. p. 107° (from ethyl acetate) (Found : C, 72·0; H, 4·9. Calc. for $C_{17}H_{14}O_4$: C, 72·3; H, 5·0%). Iyer, Shah, and Venkataraman (*loc. cit.*) give m. p. 120° for 5 : 7-dimethoxy*iso*flavone.

(*b*) 5 : 7-Dimethoxy*iso*flavone-2-carboxylic acid (0·97 g.) was heated in several portions at 230° for 1—2 min. The product was dissolved in chloroform, washed with dilute, aqueous sodium hydrogen carbonate, dried, and evaporated. The product crystallised from light petroleum (b. p. 100—120°), giving 5 : 7-dimethoxy*iso*flavone, prisms, m. p. 106—108° (0·40 g.).

2-*Carbethoxy*-5 : 7-*dimethoxy*iso*flavone.*—This was prepared (91%) by methylation of 2-carbethoxy-5 : 7-dihydroxy*iso*flavone, and formed pale yellow prisms, m. p. 159—160° (from methanol) [Found : C, 67·8; H, 5·1; (OEt)(OMe)$_2$, 28·8. $C_{16}H_7O_3(OEt)(OMe)_2$ requires C, 67·8; H, 5·1; (OEt)(OMe)$_2$, 30·2%].

o-*Ethoxalyloxyacetophenone* (with D. WEIGHT).—Ethoxalyl chloride (5 g.) was added to a solution of *o*-hydroxyacetophenone (5 g.) in anhydrous pyridine (10 c.c.) at room temperature. After ¼ hr., dilute hydrochloric acid was added, and the oil, after extraction with chloroform, was crystallised from light petroleum (b. p. 40—60°), giving o-*ethoxalyloxyacetophenone* (5·2 g.), needles, m. p. 41° (Found : C, 61·3; H, 4·8. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%). The

substance underwent hydrolysis on being kept. Basic reagents did not bring about conversion into a β-diketone (Baker–Venkataraman transformation).

Ultra-violet absorption spectra of genistein monomethyl ethers.

Compound	$\lambda_{min.}$ (log ε) (mμ)	$\lambda_{max.}$ (log ε) (mμ)	Inflection (log ε) (mμ)
7-Methyl ether (prunetin)	231 (4·07)	262·5 (4·57)	325 (3·65)
4′-Methyl ether (biochanin-A)	231 (4·10)	262·5 (4·56)	325 (3·71)
5-Methyl ether	227 (4·13)	256 (4·51)	312 (3·81)
[Genistein	231 (4·04)	263 (4·50)	325 (3·71)]

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