75. Synthetical Experiments in the isoFlavone Group. Part VII. Synthesis of Daidzein.

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The monoglucoside daidzin was isolated in 1931 by Walz (Annalen, 489, 118) from the bean Soja hispida and found to yield an aglucone, daidzein, $C_{15}H_{10}O_4$, which was shown to be 7:4'-dihydroxyisoflavone (I; R = H). Closely related to daidzin is the glucoside

ononin, first isolated from the root of the spring rest-harrow (Ononis spinosa, L.) by Reinsch (B. Repert. Pharm., 1842, 26, 12; 28, 18) and examined by Hlasiwetz (Sitzungsber. Wien. Acad., 1855, 14, 141; 15, 162; J. pr. Chem., 1855, 65, 419) and Hemmelmayr (Monatsh., 1902, 23, 134; 1903, 24, 132; 1904, 25, 555; Ber., 1900, 33, 3538). Ononin (probably II and hence $C_{22}H_{22}O_9$: the composition has been given as $C_{30}\dot{H}_{34}O_{13}$ and $C_{25}H_{26}O_{11}$) is hydrolysed by acids with formation of formononetin (I; R = Me), which in its turn is changed by boiling aqueous baryta into ononetin (III) and formic acid. The hydrolysis sequence can be reversed and in this way the glucoside, onospin, of ononetin is obtained as the intermediate stage. Formononetin thus bears the relation to daidzein that prunetin (probably) bears to genistein and ononin is (probably) the methyl ether of daidzin. The first synthesis of the ketone later shown to be identical with ononetin was effected by Baker and Eastwood (J., 1929, 2902) by an application of the Hoesch reaction. Hemmelmayr had already described the acetylation of ononetin and Wessely and Lechner (Sitzungsber. Acad. Wiss. Wien, 1930, 139, 1061) showed that the product has the constitution (IV; R = Ac) and demonstrated the identity of a specimen from ononin and one made from synthetic ononetin; they also prepared the dimethoxymethylisoflavone

(IV; R=Me). The latter substance, prepared by a slight modification of Wessely and Lechner's method, has been condensed with benzaldehyde so as to form a dimethoxy-styrylisoflavone (V; R=CH:CHPh), which has been oxidised to 7:4'-dimethoxyisoflavone-2-carboxylic acid (V; $R=CO_2H$), then decarboxylated and demethylated with formation of daidzein.

The identity of the natural and the synthetic specimen has been proved by a direct comparison, rendered possible by the courtesy of Dr. E. Walz, to whom we are greatly indebted for specimens of daidzin and daidzein.

The above method of formation of 2-styrylisoflavones takes advantage of the observation of Chakravarti (J. Indian Chem. Soc., 1931, 8, 129) that the faculty of 2-methylchromones for condensation with aldehydes is not, as has occasionally been suggested, inhibited by a methoxyl group in position 7. This represents an important improvement in the technique of the synthesis of isoflavones by way of the 2-carboxylic acids (Baker and Robinson, J., 1925, 127, 1981; 1926, 2713; 1928, 3115), a method which is still our chief resource in this group.

EXPERIMENTAL.

7: 4'-Dimethoxy-2-methylisoflavone (IV; R=Me).—In the prepn. of 7-acetoxy-4'-methoxy-2-methylisoflavone (IV; R=Ac) we followed the methods of Baker and Eastwood and of Wessely and Lechner (locc. cit.). The product crystallised from EtOH in quadrilateral plates, m. p. 193° (Found: C, 70·7; H, 5·1. Calc. for $C_{19}H_{16}O_5$: C, 70·4; H, 5·0%).

The hydrolysis (of 24 g.) was effected by heating on the steam-bath with 50% EtOH (150 c.c.) containing KOH (12 g.) for 15 min. Yield, 21 g. Stout prisms or plates, m. p. 281° after sintering at 277° (Found: C, 72·0; H, 5·0. Calc. for $C_{17}H_{14}O_4$: C, 72·1; H, 5·0%). Me₂SO₄ (9 c.c.) was added in 5 portions to a solution of this phenol (20 g.) in KOH (6 g.) and H₂O (100 c.c.) with stirring; the mixture was then heated on the steam-bath for 10 min. Yield, 19 g. The product crystallised from EtOH in flat prisms, subliming at 110° in vac., m. p. 167° (Found: C, 72·7; H, 5·5. Calc. for $C_{18}H_{16}O_4$: C, 73·0; H, 5·5%).

7: 4'-Dimethoxy-2-styrylisoflavone (V; R = CH:CHPh).—Benzaldehyde (7 g.) was added to a mixture of 7: 4'-dimethoxy-2-methylisoflavone (15 g.), EtOH (110 c.c.), and NaOEt (from 1.25 g. Na), and the whole refluxed for 2 hr. After 12 hr., the yellow ppt. (14 g.) was collected, dried, and crystallised from EtOH, forming pale yellow, microscopic, elongated prisms, m. p. 197—198° after sintering 3° lower (Found: C, 78.4; H, 5.4. $C_{25}H_{20}O_4$ requires C, 78.1; H, 5.3%). The substance exhibits the properties of its type and the solution in conc.

H₂SO₄ fluoresces greenish-yellow.

7:4'-Dimethoxyisoflavone-2-carboxylic Acid (V; R = CO₂H).—A solution of KMnO₄ (6·33 g.) in H₂O (200 c.c.) at 25° was added in 4 portions to one of the dimethoxystyrylisoflavone (5 g.) in C₅H₅N (200 c.c.) initially at 25° and kept below 40°. When all the KMnO₄ was reduced (about 10 min.), SO₂ was passed until the ppt. was white; the filtered solution was then concentrated in vac. until cloudiness appeared. Excess of dil. HCl was added, and the warm solution immediately extracted with a large vol. of EtOAc. The acid was rendered to Na₂CO₃ aq. from the org. layer and recovered by acidification. Benzoic acid was extracted from the ppt. by means of Et₂O and the new acid (yield, 0·62 g.) crystallised from EtOH in long colourless prisms, m. p. 243° (decomp.) (Found: C, 66·5; H, 4·4. C₁₈H₁₄O₆ requires C, 66·3; H, 4·3%). This acid is moderately readily sol. in hot EtOH; it develops a lemonyellow coloration in contact with conc. HCl.

7: 4'-Dimethoxyisoflavone (O-Dimethyldaidzein).—7: 4'-Dimethoxyisoflavone-2-carboxylic acid (0.6 g.) was kept at about 250° for 20 min. or until CO₂ was no longer evolved, and the residue was crystallised from EtOH (charcoal) (yield, 0.41 g.). The irregular colourless plates obtained had m. p. 155° (Found: C, 72·4; H, 5·0. Calc. for $C_{17}H_{14}O_4$: C, 72·1; H, 5·0%). Walz (loc. cit.) records the m. p. 154° for the substance prepared from daidzein.

7:4'-Dihydroxyisoflavone (Daidzein) (I; R = H).—A mixture of the dimethyl ether (0·2 g.), phenol (0·2 g.), and HI aq. (10 c.c. of b. p. 127°, d 1·7) was refluxed (bath at 150—160°) for 2 hr. The product (0·16 g.) obtained on addition of H₂O crystallised from EtOH in colourless microscopic needles which darkened at 300° and melted with slight decomp. at 312—320°. Recrystn. from 50% EtOH gave clusters of faintly yellow prisms, m. p. 315—321° (Found: C, 70·3; H, 4·2. Calc. for $C_{15}H_{16}O_4$: C, 70·9; H, 4·0%). Like many other hydroxylated flavones and isoflavones, the substance is difficult to obtain entirely solvent-free.

Walz (loc. cit.) cites the same properties, that is, darkening at 300°, m. p. 315—320°, for the pale yellow prisms of natural daidzein, cryst. from 50% EtOH. The natural and the synthetic specimen exhibited no divergences in respect of m. p., mixed m. p., and colours in dil. NaOH aq. and conc. H₂SO₄.

The diacetyl derivative prepared from the synthetic substance crystallised from EtOH in pearly-white plates and needles, m. p. 181° (Walz, loc. cit., m. p. 182° for nat. product). The m. p. was not depressed on admixture with a specimen prepared from daidzin by hydrolysis, acetylation and crystn. of the product from EtOH. The cryst. forms of the two specimens of the diacetate were observed to be identical when examined microscopically.

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