

# SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

## Part XXXIII. Synthesis of Isodaidzein and Its Methyl Ethers

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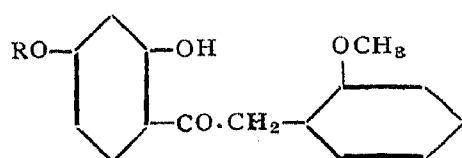
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OKANO AND BEPPU<sup>1</sup> reported that two of the crystalline components of soya beans were 2'-hydroxy isoflavone derivatives (isogenistin and 8-methyl isogenistin). Recent synthetic work<sup>2-5</sup> has proved that the structures assigned to the natural products are incorrect. However, the degradation reactions of Okano and Beppu show that 2'-hydroxy isoflavone structures are present in the naturally occurring compounds. Pterocarpin and homopterocarpin definitely contain 2'-hydroxy isoflavan structures<sup>6</sup> and rotenone and allied chromano-chromanones may be considered to be derived from 2'-hydroxy isoflavanones.<sup>7</sup> Ferreirin and homoferreirin have recently been given the constitution of isoflavanones of this type.<sup>17</sup> Though the occurrence of the simple isoflavanone nucleus in nature was reported first in the case of padmakastein (Narasimhachari and Seshadri<sup>18</sup>), ferreirin and homoferreirin are representatives of isoflavanones having a hydroxyl or methoxyl group in the 2'-position. Therefore it is reasonable to expect that simpler members of this type such as 7:2'-dihydroxy isoflavone (isodaidzein) (II a) may occur in nature. Representatives having a hydroxyl group in the 2'-position are found in the related group of flavonols, e.g., morin,<sup>8</sup> daticetin.<sup>9</sup> Further, certain special features appeared to exist in the demethylation of 2'-methoxy isoflavones.<sup>2, 4, 5</sup> The 2'-hydroxyl group in isoflavones seems to be somewhat resistant to methylation and differs from the 4'-hydroxyl group in this respect.<sup>7</sup> In order to study more fully these points, a synthesis of isodaidzein (II a) has now been undertaken.

Partial methylation of 2:4-dihydroxy-2'-methoxy phenyl benzyl ketone (I a)<sup>7</sup> gives rise to its 4-O-methyl ether (I b). Treatment of this ketone with ethyl formate and sodium at 0°,<sup>10</sup> yields 7:2'-dimethoxy isoflavone (II b). The ketone (I b) seems to be rather unreactive in this reaction and in several experiments, it is recovered unchanged. The exact conditions which would consistently lead to the formation of the isoflavone could not be determined. Another point is noteworthy. The related ketones, 2-hydroxy-4:6:2'-trimethoxy phenyl benzyl ketone<sup>4</sup> and 2-hydroxy-3-methyl-4:6:2'-trimethoxy

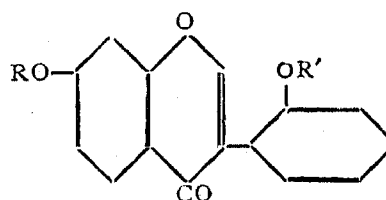
phenyl benzyl ketone<sup>5</sup> on treatment with ethyl formate and sodium yield 2-hydroxy isoflavanones which could be converted into the isoflavones subsequently.<sup>11</sup> However in the present case, the ketone (I *b*) does not yield a 2-hydroxy isoflavanone but only the isoflavone (II *b*). The formation of 2-hydroxy isoflavanones in ethyl formate condensations therefore is not a characteristic property of 2'-methoxy phenyl benzyl ketones (see also Späth and Schläger<sup>12</sup>).

Demethylation of the isoflavone (II *b*) with hydriodic acid furnished isodaidzein (II *a*) in a poor yield. The difficulties of demethylation of such 2'-methoxy isoflavones with hydriodic acid or hydrobromic acid seem to be characteristic of these compounds. However by employing aluminium chloride in benzene solution,<sup>13</sup> a good yield of isodaidzein is obtained. It does not give any colour with alcoholic ferric chloride showing that the 2'-hydroxyl group does not form part of any chelate structure. Its diacetate has also been prepared.



(I)

*a*, R = H  
*b*, R = CH<sub>3</sub>



(II)

*a*, R = R' = H  
*b*, R = R' = CH<sub>3</sub>  
*c*, R = H, R' = CH<sub>3</sub>  
*d*, R = CH<sub>3</sub>, R' = H

Formononetin<sup>14</sup> is the naturally occurring 4'-methyl ether of daidzein and similarly partial methyl ethers of isodaidzein may also be expected to occur in nature and these have now been prepared. Condensation of the ketone (I *a*) with ethyl formate and sodium gives rise to the isoflavone (I *c*). It is purified through its acetate. The preparation of this partial methyl ether (I *c*) from the dihydroxy ketone (I *a*) is analogous to the synthesis of formononetin itself which has been reported earlier.<sup>15</sup> This is another example to show that the protection of the hydroxyl group at the 4-position in the ketone of type (I *a*) before isoflavone condensation is not essential.

Treatment of isodaidzein (II *a*) with excess of methyl iodide and potassium carbonate in acetone solution furnishes predominantly the 7-methyl ether (II *d*). The behaviour of isodaidzein in this reaction is similar to that of its 2-methyl derivative, already recorded<sup>17</sup> and this shows that the hindrance to the methylation of the 2'-hydroxyl group is not due to the 2-methyl group. The negative ferric reaction in the case of isodaidzein

indicates the absence of chelation with the carbonyl of the pyrone ring and therefore the resistance of the 2'-hydroxyl group to methylation seems to be due to other factors. This partial methylation is the only convenient procedure for obtaining the 7-monomethyl ether (II *d*) since partial demethylation with acids, which has been so successful in other cases<sup>15, 16</sup> does not proceed well in the present case.

#### EXPERIMENTAL

##### *2-Hydroxy-4:2'-dimethoxy phenyl benzyl ketone (I b)*

To a solution of 2:4-dihydroxy-2'-methoxy phenyl benzyl ketone (2.5 g.) in dry acetone (100 c.c.), dimethyl sulphate (1.05 c.c.) and anhydrous potassium carbonate (3 g.) were added and the mixture refluxed for 5 hours. The acetone solution was filtered off and the potassium salts were washed with acetone. The solvent was distilled off from the filtrate. Addition of petroleum ether to the residual oil yielded a crystalline solid. This was filtered and recrystallised from alcohol. 2-Hydroxy-4:2'-dimethoxy phenyl benzyl ketone separated as thick colourless prisms melting at 93–94°. Yield 2.2 g. It gave a deep pink colour with alcoholic ferric chloride and was easily soluble in 10% aqueous sodium hydroxide (Found: C, 71.0; H, 6.0;  $C_{16}H_{16}O_4$  requires C, 70.6; H, 5.9%).

##### *7:2'-Dimethoxy isoflavone (II b)*

A solution of the ketone (1 g.) in freshly distilled ethyl formate (15 c.c.) was added to powdered sodium at 0°, gradually with shaking in the course of 30 minutes. The mixture was left in the refrigerator for 48 hours. Pieces of ice were added and after allowing the ethyl formate to evaporate, the mixture was extracted with ether. The ether solution was washed with aqueous sodium hydroxide (10%) to remove unchanged ketone and then with water and finally evaporated. The residue, when crystallised twice from alcohol, yielded 7:2'-dimethoxy isoflavone as colourless rectangular rods melting at 111–12°. The yield varied considerably and in many condensations, most of the ketone was recovered. The maximum yield obtained in any experiment was about 55% (Found: C, 72.3; H, 5.3;  $C_{17}H_{14}O_4$  requires C, 72.4; H, 5.0%).

##### *7:2'-Dihydroxy isoflavone (Isodaidzein) (II a)*

(i) To a solution of the above dimethoxy isoflavone (0.8 g.) in acetic anhydride (14 c.c.) was added hydriodic acid (20 c.c.) and the mixture heated in an oil-bath at 140–50° for 2 hours. It was cooled and diluted with saturated aqueous sodium bisulphite (60 c.c.). The dark solid that

separated overnight, was filtered and crystallised from dilute alcohol (Norit) twice, when 7:2-dihydroxy isoflavone separated as thick colourless long rectangular prisms melting at 208°<sub>9</sub>. Yield 60 mg. It was easily soluble in alcohol and dilute aqueous sodium carbonate and it did not give any colour with ferric chloride in alcoholic solution. Found: C, 71.0; H, 4.1;  $C_{15}H_{10}O_4$  requires C, 70.9; H, 3.9%.

(ii) 7:2-Dimethoxy isoflavone (0.45 g.) was dissolved in dry benzene (30 c.c.) and powdered anhydrous aluminum chloride (1.3 g.) added. The mixture was refluxed for 2 hours in a water bath. Benzene was then distilled off and the aluminum chloride complex decomposed by the addition of ice and hydrochloric acid (10 c.c.). The grey solid that was obtained was filtered after 8 hours and was repeatedly macerated with aqueous sodium carbonate (10%). A small amount of insoluble matter was filtered off. The filtrate on acidification yielded a colourless solid which when crystallised from dilute alcohol gave 7:2-dihydroxy isoflavone as colourless rectangular prisms melting at 208°<sub>9</sub> alone or when mixed with a sample described in (i) above. Yield 0.2 g.

The diacetate, prepared by acetylation with acetic anhydride and pyridine, crystallised from alcohol as colourless thick rectangular tablets melting at 144-45°. It was easily soluble in hot alcohol (Found: C, 67.7; H, 4.4;  $C_{19}H_{14}O_6$  requires C, 67.5; H, 4.3%.)

#### *7-Hydroxy-2'-methoxy isoflavone (II c)*

A solution of 2'-4-dihydroxy-2'-methoxy phenyl benzyl ketone (1.3 g.) in ethyl formate (20 c.c.) was added to powdered sodium (1 g.) at 0° and kept for 48 hours at the same temperature. Ice and hydrochloric acid were then added, the unreacted ethyl formate was evaporated off and the pale yellow solid filtered and washed with water. It melted at about 165° and gave a positive ferric reaction and was therefore a mixture of the unchanged ketone and the isoflavone. The pure isoflavone could not be obtained by crystallisation and the mixture was therefore acetylated with acetic anhydride and pyridine. The product when crystallised twice from alcohol yielded 7-acetoxy-2'-methoxy isoflavone as long thin colourless rectangular plates tapering at one end and melting at 137°<sub>9</sub>. (Found: C, 69.3; H, 4.2;  $C_{18}H_{14}O_5$  requires C, 69.7; H, 4.5%.)

The above acetate (0.15 g.) was dissolved in a mixture of alcohol (8 c.c.) and concentrated hydrochloric acid (8 c.c.) and the solution boiled in a water-bath for 15 minutes. It was diluted with water and the alcohol distilled off. The colourless crystals that separated on cooling were collected and recrystallised from alcohol twice when 7-hydroxy-2'-methoxy

isoflavone was obtained in the form of sheaves of colourless plates melting at 230–32°. It was soluble in dilute aqueous sodium carbonate and did not give any colour with alcoholic ferric chloride (Found: C, 71.6; H, 4.9;  $C_{16}H_{12}O_4$  requires C, 71.6; H, 4.5%).

*Methylation of 7:2'-dihydroxy isoflavone (II a)*

7:2'-Dihydroxy isoflavone (0.7 g.) was dissolved in acetone (100 c.c.) and the solution refluxed with methyl iodide (4 c.c.) and potassium carbonate (5 g.) for 3 hours on a water-bath. The acetone solution was filtered and the potassium salts were washed with warm acetone. The residue left on distilling off the solvent from the combined filtrate was taken up in ether. The ether solution was extracted with aqueous sodium hydroxide (10%) thrice. The precipitate obtained on acidification of the alkaline solution was filtered and crystallised twice from alcohol, when 7-methoxy-2'-hydroxy isoflavone (II d) separated as stout colourless rectangular prisms melting at 148°. Yield 0.4 g. (Found: C, 71.7; H, 4.6;  $C_{16}H_{12}O_4$  requires C, 71.6; H, 4.5%). The acetate, prepared by the acetic anhydride-pyridine method, crystallised from alcohol as colourless plates and prisms melting at 134–35° (Found: C, 70.0; H, 4.2;  $C_{18}H_{14}O_5$  requires C, 69.7; H, 4.5%).

The original ether solution left after extraction with alkali was washed with water and evaporated. The residue crystallised from alcohol as colourless rectangular rods melting at 111–12° alone or when mixed with a sample of 7:2'-dimethoxy isoflavone (II b) described earlier. Yield 30 mg.

SUMMARY

The synthesis of isodaidzein and of its methyl ethers has been carried out and their properties studied. The special features noticed earlier in the case 2'-hydroxy isoflavones are also found here and they seem to be characteristic of the presence of the 2'-methoxy and hydroxy groups in isoflavones.

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