

SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part XVI. Isoformononetin and Its Derivatives

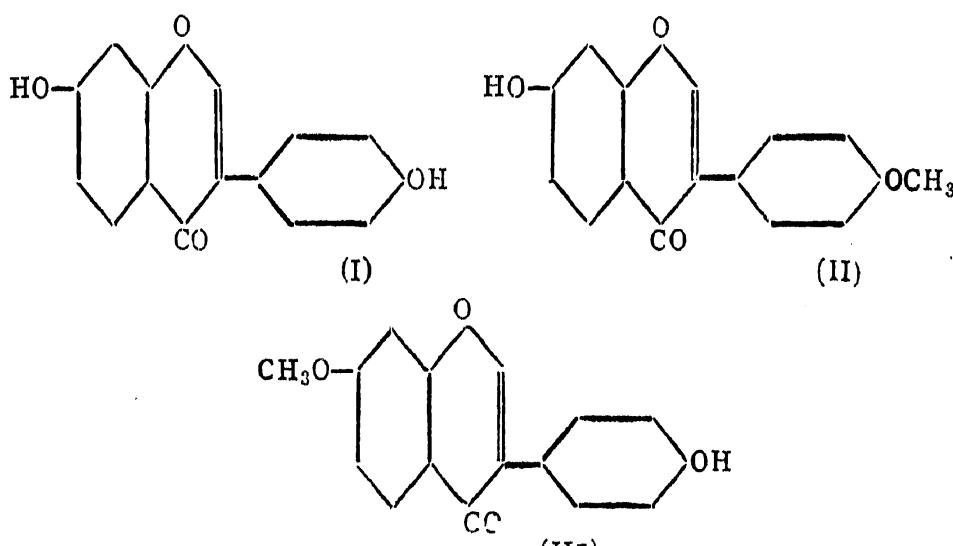
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IN two previous parts of this series¹ earlier experiments on the scope of partial methylation and demethylation for the preparation of 7-methyl ethers of isoflavones were reported with reference to the synthesis of prunetin and santal. The results were quite encouraging and both these naturally occurring 7-methyl ethers were prepared. In support of the theoretical considerations involved, it was felt that simpler cases should be studied in detail and the scope of the method fully understood. Hence the experiments described in this paper were undertaken.

Of the two monomethyl ethers of daidzein (I), formononetin, the 4'-methyl ether (II) was first found to occur in nature.² This was first synthesised in poor yield by Wessely *et al.*³ by heating 2:4-dihydroxy-4'-methoxy-phenyl-benzyl ketone with sodium and ethyl formate in a sealed tube at 100°. Subsequently Mahal, *et al.*⁴ employed 2-hydroxy-4-benzyloxy-4'-methoxy-phenyl-benzyl ketone instead of the dihydroxy compound and carried out the reaction at 0° and finally effected the removal of benzyl group. The protection of the 4-hydroxyl group in the ketone is not necessary and a good yield of formononetin has now been obtained directly from the dihydroxy ketone using the low temperature (0°) for the reaction.



The isomeric 7-monomethyl ether of daidzein which is now named isoformononetin (III) has not so far been made or described. For its preparation we have employed the partial methylation of daidzein using one mole of dimethyl sulphate. The product is a mixture which could be separated into the following fractions: (1) carbonate soluble; (2) carbonate insoluble but sodium hydroxide soluble; (3) sodium hydroxide insoluble. Fraction (1) obtained by acidifying the carbonate solution consisted of pure daidzein and no formononetin seemed to be present in it. Fraction (2) precipitated from sodium hydroxide solution by acid yielded isoformononetin and fraction (3) which was rather small yielded dimethyl daidzein. The results are in accordance with the theoretical considerations discussed in Part XIII.¹

The method of partial demethylation was next investigated using O-dimethyl daidzein and hydrobromic acid and hydriodic acid; under suitable conditions almost quantitative yields of isoformononetin could be obtained with these reagents. Heating with hydriodic acid at 120° for half an hour seems to offer the most satisfactory method of partial demethylation for obtaining the 7-methyl ethers of isoflavones.

5:7-Dihydroxy and dimethoxy isoflavones offer the simplest examples for the study of partial methylation and demethylation. Based on analogy with similar flavones and flavanones the existence of large difference between the two hydroxyl groups could be readily understood as also the possibility of partial methylation of the 7-hydroxyl group. For obtaining the 7-methyl ether by demethylation, mild demethylating agents would normally be suggested just as in the case of chrysanthemum dimethyl ether. But in view of our experience with other isoflavones we have now carried out this partial demethylation using hydriodic acid and the method works quite satisfactorily.

5:7-Dihydroxy isoflavone and its methyl ethers were not described till the present work had been completed and the recent paper of Iyer *et al.*⁵ containing this description appeared only in March this year. Since our methods and results are slightly different, they are reported in this paper.

2-Hydroxy-4:6-dimethoxy-phenyl-benzyl ketone is conveniently made from phloroglucinol trimethyl ether and phenyl acetyl chloride by condensation in presence of anhydrous aluminium chloride. The product agrees in all its properties with that described by Badcock, *et al.*⁶ and Iyer, *et al.*⁵ who have made it by a different route. The subsequent isoflavone condensation proceeds quite smoothly giving rise to high yields of 5:7-dimethoxy isoflavone. Partial demethylation of this dimethyl ether with hydriodic acid

gives a very high yield of the 7-monomethyl ether. The interesting point that should be mentioned here is that in the analogous case of chrysindimethyl ether using similar conditions the product is found to be mostly chrysin. This reveals the existence of marked difference in the stability of the 7-methyl ether groups in flavones and isoflavones. The explanation is to be found in the difference in the location of the side phenyl nucleus in the two groups of compounds. In flavones the demands of the pyrone C=O group for electrons are met by both the phenyl nuclei whereas in isoflavones the side phenyl plays no part. Consequently in the latter, the 7-position receives a higher quantum of positive charge making this particular hydroxyl more strongly acidic and the methoxyl more firmly held.

EXPERIMENTAL

Formononetin.—Powdered sodium (1 g.) was cooled in ice and treated with a solution of 2:4-dihydroxy-4'-methoxy-phenyl-benzyl ketone (2 g.) in ethyl formate (10 c.c.) with shaking. After keeping in the refrigerator for 48 hours pieces of ice were added and the excess of ethyl formate was removed under reduced pressure. On acidifying the cooled solution formononetin separated as colourless solid and crystallised from alcohol as colourless prisms melting at 255-57°.³ It dissolved readily in aqueous sodium carbonate solution and gave no colour with ferric chloride in alcoholic solution.

Daidzein.—This was obtained by demethylating formononetin with hydriodic acid (d. 1.7) at 140° for one hour. It crystallised from alcohol as colourless prisms melting at 320-22°. The diacetate crystallised from ethyl acetate as clusters of needles melting at 184-6°.⁴

Partial methylation (7-Methoxy-4'-hydroxy isoflavone, isoformononetin).—To a solution of daidzein (0.9 g.) in acetone (100 c.c.) dimethyl sulphate (0.35 c.c.) and potassium carbonate (1 g.) were added and the mixture refluxed for three hours. Acetone was then distilled off and the residue treated with water. The solid that separated was filtered and macerated with sodium carbonate. The residue was then treated with sodium hydroxide solution and the insoluble dimethyl ether was separated by filtration. The dimethyl ether (50 mg.) crystallised from alcohol as colourless needles melting at 154-56°. The alkali solution on acidification gave a colourless solid which crystallised from alcohol as long stout elongated rectangular prisms melting at 218-20°. It was insoluble in cold sodium carbonate solution and gave no colour with ferric chloride in alcoholic solution. Yield, 0.4 g. (Found: C, 71.2; H, 4.5; $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.5%).

The carbonate solution on acidification gave a colourless solid melting above 310° and one crystallisation from alcohol gave pure daidzein, m.p. 320-22°.

Acetate.—7-Methoxy-4'-hydroxy isoflavone obtained above was acetylated by refluxing with acetic anhydride and pyridine for one hour. The acetate crystallised from ethyl acetate as colourless plates and prismatic needles melting at 148-49° (Found: C, 69.4; H, 4.4; $C_{18}H_{14}O_5$ requires C, 69.7; and H, 4.5%).

On deacetylation with alcoholic hydrochloric acid and crystallisation from alcohol the isoflavone melted at 218-20°.

7: 4'-Dimethoxy isoflavone.—2:4-Dihydroxy-4'-methoxy-phenyl-benzyl ketone required for this purpose was prepared following the method of Baker and Eastwood,⁷ using resorcinol and *p*-methoxy-benzyl cyanide. This was methylated to 2-hydroxy-4:4'-dimethoxy-phenyl-benzyl ketone using dimethyl sulphate (1 mole) and anhydrous potassium carbonate in acetone solution. It (1 g.) was dissolved in ethyl formate (6 c.c.) and the solution added to pulverised sodium (0.5 g.), cooled in ice and the mixture left in the refrigerator for 48 hours. Crushed ice was then added and ethyl formate removed under reduced pressure. On leaving overnight a colourless solid separated out. It was filtered and the filtrate acidified when some more of the product was obtained. 7:4'-Dimethoxy isoflavone crystallised from alcohol as colourless needles melting at 154-56°, was insoluble in aqueous sodium hydroxide and gave no colour with ferric chloride.

Partial demethylation

(i) *With hydrobromic acid.*—7:4'-Dimethoxy isoflavone (0.3 g.) was dissolved in glacial acetic acid (5 c.c.) and heated with hydrobromic acid (d. 1.51; 10 c.c.) for 2 hours on a boiling water-bath. The mixture was then diluted with ice-water and the solid that separated was filtered and washed with water. It was then dissolved in 5% aqueous sodium hydroxide, the solution filtered and the cold alkaline solution acidified with hydrochloric acid. On crystallising from alcohol the product was obtained as colourless long rectangular prisms melting at 218-20°. It was identical with 7-methoxy-4'-hydroxy isoflavone in its properties and a mixed melting point with the sample described above was undepressed.

(ii) *With hydriodic acid.*—7:4'-Dimethoxy isoflavone (0.4 g.) was dissolved in acetic anhydride (4 c.c.) and treated with cooling with hydriodic acid (10 c.c.; d. 1.7). The solution was heated in an oil-bath at 120° for half an hour. It was then diluted with water, iodine decolourised with

sulphurous acid and left in the refrigerator overnight. The solid that separated was filtered, washed with water and macerated with sodium carbonate solution. The residue was then dissolved in aqueous sodium hydroxide and the clear solution acidified. The product crystallised from alcohol as colourless stout rectangular prisms melting at 218° and was identical with 7-methoxy-4'-hydroxy isoflavone; the mixed melting point with the above two samples was undepressed. Yield, 0.25 g. The acetate crystallised from ethyl acetate as colourless needles and melted at 148–49° alone or in admixture with the other samples already described. The sodium carbonate extract on acidification gave a very small quantity of daidzein.

7-Methoxy-4'-ethoxy isoflavone.—7-Methoxy-4'-hydroxy isoflavone (0.1 g.) was refluxed in acetone solution with excess of ethyl iodide and anhydrous potassium carbonate for 6 hours. The ethyl ether crystallised from dilute alcohol as colourless short stout prisms melting at 121–22°. It was insoluble in aqueous alkali and gave no colour with ferric chloride in alcoholic solution (Found: C, 73.4; H, 5.2; $C_{18}H_{16}O_4$ requires C, 73.0; H, 5.4%).

Ethylation of formononetin (7-ethoxy-4'-methoxy isoflavone)

Formononetin (0.1 g.) was ethylated as described above. Ethyl formononetin crystallised from alcohol as colourless stout rectangular prisms melting at 141–42° (Found: C, 72.8; H, 5.6; $C_{18}H_{16}O_4$ requires C, 73.0; H, 5.4%).

2-Hydroxy-4:6-dimethoxy-phenyl-benzyl ketone.—Phloroglucinol trimethyl ether required for this purpose was conveniently obtained by the dry methylation of phloroglucinol with dimethyl sulphate (3 moles) and anhydrous potassium carbonate in acetone solution.

To a solution of anhydrous aluminium chloride (12 g.) and phloroglucinol trimethyl ether (5 g.) in dry ether (100 c.c.) cooled in ice, phenyl acetyl chloride (4 c.c.) was added drop by drop with shaking. The mixture was allowed to stand in the ice-bath for half an hour and then at room temperature for 24 hours. Ether was distilled off and the residue treated with ice and concentrated hydrochloric acid. After warming on a water-bath for 15 minutes the mixture was cooled. The oily liquid soon solidified. It was filtered and washed with dilute hydrochloric acid. The residue was dissolved in aqueous sodium hydroxide and when the solution was acidified it gave a colourless solid. On crystallisation from alcohol it separated as colourless prisms and melted at 117–18°.^{5,6} It gave a reddish brown colour with ferric chloride and a blue colour with concentrated nitric acid.

5:7-Dimethoxy isoflavone.—The above ketone (1 g.) was dissolved in ethyl formate (5 c.c.) and cooled in ice. Powdered sodium (0.5 g.) cooled in ice, was then added in small quantities and the mixture left in the refrigerator for 48 hours. Crushed ice was added and excess ethyl formate removed under reduced pressure. On cooling, the oily liquid soon solidified. It crystallised from alcohol as small prisms and melted at 121–2°. Some more of it could be obtained by acidifying the aqueous solution. Yield 0.6 g. Iyer, *et al.*⁵ gave its melting point as 120°.

5:7-Dihydroxy isoflavone.—This was obtained by demethylating the dimethoxy compound with hydriodic acid for 3 hours at 140° in an oil-bath. 5:7-Dihydroxy isoflavone crystallised from alcohol as colourless prisms melting at 192–4°. It readily dissolved in aqueous sodium carbonate and gave a pink colour with ferric chloride. Its properties agreed with the description of Iyer, *et al.*⁵

5-Hydroxy-7-methoxy isoflavone

(1) *Partial methylation.*—On methylating with one mole of dimethyl sulphate and anhydrous potassium carbonate in acetone solution for 3 hours 5:7-dihydroxy isoflavone gave the 7-methyl ether. It crystallised from ethyl acetate as colourless rectangular prisms melting at 140–41°. It gave a red colour with ferric chloride and was sparingly soluble in aqueous sodium hydroxide.

(2) *Partial demethylation.*—5:7-Dimethoxy isoflavone (0.4 g.) was heated with acetic anhydride (5 c.c.) and hydriodic acid (10 c.c.) at 120° for half an hour and the product worked up as usual. It was macerated with sodium carbonate solution and the residue crystallised. It separated from ethyl acetate in the form of colourless stout rectangular prisms and melted at 141°. (Found: C, 71.2; H, 4.3; $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.5%). It agreed in all its properties with the sample obtained by method (1) and a mixed melting point was undepressed. The carbonate washings when acidified did not yield any 5:7-dihydroxy isoflavone.

The above samples agreed with the description of Iyer *et al.*⁵

SUMMARY

The study of daidzein derivatives provides further support to the conclusions already arrived at regarding the special features of partial methylation and demethylation in the isoflavone series. Partial methylation of daidzein gives a good yield of the 7-monomethyl ether (isoformononetin) and the formation of the isomeric formononetin could not be detected. The

same 7-methyl ether is obtained most conveniently by the demethylation of daidzein dimethyl ether with hydrobromic acid and hydriodic acid. 5:7-Dihydroxy and di-methoxy isoflavones have also been examined with a view to compare them with corresponding flavones. 7-Methoxy-5-hydroxy isoflavone is obtained most readily by partial demethylation of dimethoxy isoflavone with hydriodic acid whereas chrysin dimethyl ether yields mostly chrysin under these conditions.

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