Tetrahedron, 1959, Vol. 7, pp. 77 to 81. Pergamon Press Ltd. Printed in Northern Ireland

RING-ISOMERIC CHANGE IN ISOFLAVONES

SYNTHESIS OF 5,7-DIMETHOXY-6-HYDROXYISOFLAVONE, MUNINGIN AND 5,7-DIHYDROXY-6-METHOXYISOFLAVONE

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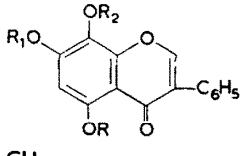
(*Received* 10 *January* 1959; *in revised form* 6 *March* 1959)

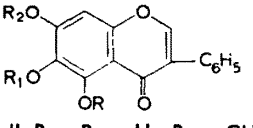
Abstract—The above mentioned compounds have been prepared by methods involving isomeric change from the more readily available 5,7,8-substituted isoflavones.

RING isomeric change in flavonoids, the Wessely-Moser rearrangement[1] has been investigated in detail in recent years.[2] The rearrangement takes place with chromones and flavones in strongly acid medium but does not proceed satisfactorily in the case of isoflavones. Isoflavones isomerise under alkaline conditions[3] and Mahesh and Seshadri[4] showed that 5-hydroxy-7,8-dimethoxyisoflavone can be converted into the isomeric 5-hydroxy-6,7-dimethoxyisoflavone by treatment with alcoholic potash. This is useful because the former is more easily prepared. This method of isomeric change has now been applied for the synthesis of a few isoflavones substituted in the 5,6,7-positions and belonging to the types occurring in nature.

5,8-Dihydroxy-7-methoxyisoflavone[5] (I) was obtained by the controlled demethylation of 5,7,8-trimethoxyisoflavone with hydriodic acid. It isomerized in alcoholic potash giving poor yields of 5,6-dihydroxy-7-methoxy-isoflavone (II)[6,7]; better yields were obtained in a hydrogen atmosphere. 8-Benzyloxy-5-hydroxy-7-methoxyisoflavone (III) obtained by the partial benzylation of the dihydroxy isoflavone (I) gave satisfactory yields of 6-benzyloxy-5-hydroxy-7-methoxyisoflavone (IV). It was then methylated to give 6-benzyloxy-5,7-dimethoxyisoflavone (V) which on debenzylation with hydrogen and Raney-nickel gave 6-hydroxy-5,7-dimethoxy isoflavone[8] (VI); hydrochloric acid was unsuitable since it produced demethylation in the 5-position.



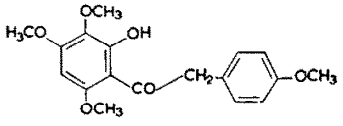
I, $R = R_2 = H$; $R_1 = CH_3$
III, $R = H$; $R_1 = CH_3$; $R_2 = C_7H_7$



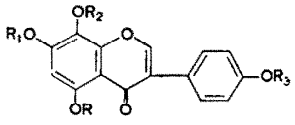
II, $R = R_1 = H$; $R_2 = CH_3$
IV, $R = H$; $R_1 = C_7H_7$; $R_2 = CH_3$
V, $R = R_2 = CH_3$; $R_1 = C_7H_7$
VI, $R = R_2 = CH_3$; $R_1 = H$

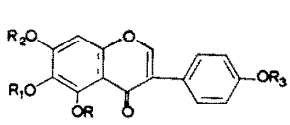
[1] F. Wessely and G. H. Moser, *Monatsh.* **56**, 97 (1930).
[2] S. K. Mukerjee and T. R. Seshadri, *Chem. & Ind.* 271 (1955).
[3] V. B. Mahesh, N. Narasimhachari and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **39 A**, 165 (1954).
[4] V. B. Mahesh and T. R. Seshadri, *J. Sci. Industr. Res. India* **14 B**, 671 (1955).
[5] Ishwar Dass, N. Narasimhachari and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **37 A**, 599 (1953).
[6] S. S. Karmarkar, K. M. Shah and K. Venkataraman, *Proc. Ind. Acad. Sci.* **41 A**, 192 (1955).
[7] K. Aghoramurthy, T. R. Seshadri and G. B. Venkatasubramanian, *J. Sci. Industr. Res.* **15 B**, 11 (1956).
[8] M. L. Dhar and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **43 A**, 79 (1956).

For the synthesis of muningin, the intermediate 2-hydroxy-3,4,6,4′-tetramethoxyphenylbenzyl ketone (VII) was prepared by the Friedel and Crafts reaction using 1,2,3,5-tetramethoxybenzene and *p*-methoxyphenylacetyl chloride. Ring closure using the ethyl formate and sodium method[9] yielded 5,7,8,4′-tetramethoxyisoflavone (VIII) which on partial demethylation with hydriodic acid[5] gave 5,8,4′-trihydroxy-7-methoxyisoflavone (IX). Benzylation gave 8,4′-dibenzyloxy-5-hydroxy-7-methoxyisoflavone (X) which isomerized into 6,4′-dibenzyloxy-5-hydroxy-7-methoxyisoflavone (XI). Subsequent methylation gave muningin dibenzyl ether (XII) and final debenzylation yielded muningin (XIII), identical with the natural sample[10] and also that synthesized previously.[8]



VII

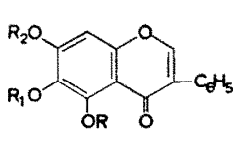


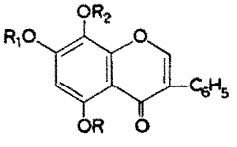


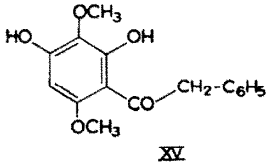
VIII, R = R_1 = R_2 = R_3 = CH_3
IX, R = R_2 = R_3 = H; R_1 = CH_3
X, R = H; R_1 = CH_3; R_2 = R_3 = C_7H_7

XI, R = H; R_2 = CH_3; R_1 = R_3 = C_7H_7
XII, R = R_2 = CH_3; R_1 = R_3 = C_7H_7
XIII, R = R_2 = CH_3; R_1 = R_3 = H

In view of the difficulties originally experienced in the synthesis of tectorigenin, it was considered useful to extend the method of ring isomeric change for its synthesis. In exploratory experiments the simpler analogue, 5,7-dihydroxy-6-methoxyisoflavone (XIV) has been synthesized successfully. 2,4-Dihydroxy-3,6-dimethoxyphenylbenzyl ketone (XV) was obtained by the Hoesch reaction of 2,6-dibenzyloxy-1,4-dimethoxybenzene and phenylacetonitrile and converted into 7-hydroxy-5,8-dimethoxyisoflavone (XVI). Partial demethylation with anhydrous aluminium chloride or concentrated hydrochloric acid gave 5,7-dihydroxy-8-methoxyisoflavone (XVII) which on treatment with alcoholic potash isomerized to 5,7-dihydroxy-6-methoxyisoflavone (XIV). It was also prepared from 5,6,7-trihydroxyisoflavone which was benzylated in the 7-position (XVIII) followed by partial methylation (XIX) and dedenzylation with acetic acid and hydrochloric acid. Isomerization has not so far been successful in the case of the corresponding 4′-hydroxy substituted isoflavone and tectorigenin was not obtained.







XV

XIV, R = R_2 = H; R_1 = CH_3
XVIII, R = R_1 = H; R_2 = C_7H_7
XIX, R = H; R_1 = CH_3; R_2 = C_7H_7

XVI, R = R_2 = CH_3; R_1 = H
XVII, R = R_1 = H; R_2 = CH_3

EXPERIMENTAL

5,6-Dihydroxy-7-methoxyisoflavone (II)

A solution of 5,8-dihydroxy-7-methoxyisoflavone[5] (1 g) in alcoholic potash (100 cc, 2%) was refluxed for ½ hr under hydrogen, cooled to 0°, acidified with HCl and the precipitated isoflavone

[9] P. C. Joshi and K. Venkataraman, *J. Chem. Soc.* 513 (1934).
[10] F. E. King, T. J. King and A. J. Warwick, *J. Chem. Soc.* 96 (1952).

collected and crystallized from alcohol; colourless silky needles (0·15 g) m.p. and mixed m.p. with an authentic sample[8] 222–224°.

8-Benzyloxy-5-hydroxy-7-methoxyisoflavone (III)

5,8-Dihydroxy-7-methoxyisoflavone (3 g) in dry acetone (300 cc) was treated with benzyl chloride (1·2 cc) anhydrous potassium carbonate (10 g) and anhydrous sodium iodide (2·5 g) and the mixture refluxed for 9 hr. The *benzyloxy isoflavone* crystallized from alcohol as colourless rectangular prisms (1·9 g), m.p. 106–108°. It gave a green colour with ferric chloride and was sparingly soluble in 5% aqueous sodium hydroxide (Found: C, 74·2; H, 5·1; $C_{23}H_{18}O_5$ requires: C, 73·7; H, 4·8%).

6-Benzyloxy-5-hydroxy-7-methoxyisoflavone (IV)

III (1 g) was isomerized with alcoholic potash (100 cc; 2%) as before but without hydrogen. The *isoflavone* crystallized from alcohol as colourless rhombohedral plates (0·5 g) m.p. 174–176°. The mixed m.p. with an authentic sample of 6-benzyloxy-5-hydroxy-7-methoxy isoflavone prepared by the partial benzylation of 5,6-dihydroxy-7-methoxy isoflavone showed no depression. It gave a green colour with ferric chloride and was sparingly soluble in 5% aqueous sodium hydroxide (Found: C, 73·2; H, 4·6; $C_{23}H_{18}O_5$ requires: C, 73·7; H, 4·8%).

6-Benzyloxy-5,7-dimethoxyisoflavone (V)

Prepared by the methylation of 6-benzyloxy-5-hydroxy-7-methoxyisoflavone using methyl sulphate, acetone and potassium carbonate, the *methyl ether* was obtained as small rectangular prisms from alcohol m.p. 154–155°. It gave no colour with ferric chloride and was insoluble in aqueous sodium hydroxide (Found: C, 73·7; H, 5·4; $C_{24}H_{20}O_5$ requires: C, 74·2; H, 5·1%).

6-Hydroxy-5,7-dimethoxyisoflavone (VI)

The methyl ether (V) (0·5 g) in alcohol (300 cc) was treated with Raney nickel (1·5 g) and a slow stream of hydrogen was passed for ½ hr with occasional shaking. The solution was filtered and the filtrate evaporated under reduced pressure. The residue crystallized from dilute alcohol yielding the *isoflavone* as colourless thick rectangular tablets and plates (0·15 g) m.p. 184–186°. It was easily soluble in dilute aqueous sodium hydroxide (Found: C, 68·1; H, 5·0; $C_{17}H_{14}O_5$ requires: C, 68·4; H, 4·7%). The *acetate* crystallized from alcohol as colourless thick rectangular tablets, m.p. 205–207°.[8]

2-Hydroxy-3,4,6,4′-tetramethoxyphenylbenzyl ketone (VII)

To a solution of anhydrous aluminium chloride (20 g) in ether (200 cc) at 0°, 1,2,3,5,-tetramethoxy benzene (10 g) in ether was added, followed by *p*-methoxyphenylacetyl chloride (8 cc). The mixture was cooled in ice for 2 hr and subsequently left at room temp for 12 hr. Ether was removed and the residue decomposed with ice and HCl and heated (water-bath) for 1 hr. The ketone separated as an oil on cooling and was extracted with ether, and the ether solution washed first with aqueous sodium bicarbonate, and then with water and finally dried over anhydrous sodium sulphate.

Evaporation of ether gave the *ketone* as a dark viscous mass which crystallized from alcohol as pale yellow prisms (9·0 g) m.p. 119–120°. It gave a reddish brown colour with alcoholic ferric chloride (Found: C, 65·3; H, 6·1; $C_{18}H_{20}O_6$ requires: C, 65·0; H, 6·0%).

5,7,8,4′-Tetramethoxyisoflavone (VIII)

Prepared from VII (2 g) by cyclization with ethyl formate (20 cc) in presence of powdered sodium (1 g), the *isoflavone* was obtained from ethyl acetate as long rectangular tablets (1·0 g) m.p. 147–149° (Found: C, 66·2; H, 5·3; $C_{19}H_{18}O_6$ requires: C, 66·6; H, 5·2%).

5,8,4′-Trihydroxy-7-methoxyisoflavone (IX)

Tetramethoxy isoflavone (VIII, 1 g) in acetic anhydride (10 cc) was heated with hydriodic acid (10 cc, *d* 1·7) at 120° for ½ hr. After cooling and decolourizing with sulphurous acid, the solid was collected and crystallized from alcohol yielding pale yellow rectangular plates of the *isoflavone* (0·6 g) m.p. 268–270° (*d*) with sintering at 240°. It gave a green colour with alcoholic ferric chloride and was easily soluble in aqueous sodium carbonate (Found: C, 63·9; H, 3·9; $C_{16}H_{12}O_6$ requires: C, 64·0; H, 4·0%).

8,4′-*Dibenzyloxy-5-hydroxy-7-methoxyisoflavone* (X)

A solution of IX was partially benzylated with benzyl chloride (2 moles) as described before, and the *dibenzyl ether* crystallized from ethyl acetate–light petroleum as colourless rhombohedral tablets (0·5 g) m.p. 102–104°. It gave an olive green colour with alcoholic ferric chloride and was sparingly soluble in aqueous sodium hydroxide (Found: C, 74·6; H, 4·9; $C_{30}H_{24}O_6$ requires: C, 75·0; H, 5·0%).

6,4′-*Dibenzyloxy-5-hydroxy-7-methoxyisoflavone* (XI)

X (0·5 g) was isomerized with alcoholic potash (50 cc, 2%). The *isoflavone* (XI) crystallized from alcohol as colourless rectangular prisms (0·25 g) m.p. 182–184°. It gave a green colour with alcoholic ferric chloride and was sparingly soluble in aqueous sodium hydroxide (Found: C, 74·8; H, 5·2; $C_{30}H_{24}O_6$ requires: C, 75·0; H, 5·0%).

6,4′-*Dibenzyloxy*-5,7-*dimethoxyisoflavone* (XII)

Prepared by the methylation of XI (0·5 g) with excess of dimethyl sulphate, acetone and potassium carbonate, the *benzyl methyl ether* crystallized from alcohol as colourless rectangular rods (0·3 g) m.p. 246° (*d*) (Found: C, 74·9; H, 5·7; $C_{31}H_{26}O_6$ requires: C, 75·3; H, 5·2%).

6,4′-*Dihydroxy*-5,7-*dimethoxyisoflavone* (*muningin* XIII)

The above benzyl methyl ether (0·5 g) in alcohol (700 cc) was debenzylated with Raney nickel (1·5 g) and hydrogen. The *hydroxy isoflavone* crystallized from dioxan as colourless rectangular tablets (0·1 g) m.p. 285°. It gave no colour with alcoholic ferric chloride and dissolved in aqueous alkali giving a yellow solution which turned red on heating. It also developed a red colour with conc H_2SO_4 and a trace of conc HNO_3. It was identical with a natural sample of muningin[10] and mixed m.p. was undepressed (Found: C, 64·5; H, 4·8; $C_{17}H_{14}O_6$ requires: C, 65·0; H, 4·5%). The *acetate* crystallized from alcohol as colourless needles m.p. 230–232° agreeing with an authentic sample.

7-*Benzyloxy*-5,6-*dihydroxyisoflavone* (XVIII)

5,6,7-Trihydroxy isoflavone (2 g) in dry acetone (200 cc) was refluxed with benzyl chloride (0·84 cc, 1 mole), sodium iodide (1 g) and sodium bicarbonate (6 g) for 24 hr. The *benzyl ether* crystallized from alcohol as colourless long needles (0·7 g) m.p. 234–236°. It gave a green colour with alcoholic ferric chloride (Found: C, 73·4; H, 4·9; $C_{23}H_{16}O_5$ requires: C, 73·3; H, 4·4%).

7-*Benzyloxy*-5-*hydroxy*-6-*methoxyisoflavone* (XIX)

XVIII (1 g), dry acetone (200 cc), dimethylsulphate (0·22 cc, 1 mole) and anhydrous potassium carbonate (5 g) were heated for 6 hr. The *methyl ether* crystallized from alcohol as rectangular prisms (0·6 g) m.p. 184–186° and gave a reddish violet colour with alcoholic ferric chloride (Found: C, 73·4; H, 4·9; $C_{23}H_{18}O_5$ requires: C, 73·7; H, 4·8%).

5,7-*Dihydroxy*-6-*methoxyisoflavone* (XIV)

XIX (0·4 g) was debenzylated by heating with glacial acetic acid (30 cc) and conc HCl (4 cc) for 1½ hr. The *hydroxy isoflavone* crystallized from ethyl acetate–light petroleum as long prismatic needles (0·2 g) m.p. 154–156°. It was soluble in aqueous sodium carbonate (5%) and gave a reddish violet colour with ferric chloride which changed to deep green with excess of the reagent (Found: C, 67·3; H, 4·3; $C_{16}H_{12}O_5$ requires: C, 67·6; H, 4·2%). The *acetate* was obtained from alcohol as colourless needles, m.p. 162–164° (Found: C, 64·6; H, 4·7; $C_{20}H_{16}O_7$ requires: C, 65·2; H, 4·3%).

2,4-*Dihydroxy*-3,6-*dimethoxyphenylbenzyl ketone* (XV)

Dry hydrogen chloride was passed through a mixture of 2,6-dibenzyloxy-1,4-dimethoxy benzene (10 g), zinc chloride (4 g) and benzyl cyanide (3·4 cc) in dry ether (150 cc), cooled in a freezing mixture. After 2 hr the freezing mixture was replaced by ice and the passage of hydrogen chloride continued for another 6 hr. The mixture was left in the ice chest for 2 days; the oily ketimine hydrochloride was washed with ether, dissolved in hot water, the solution allowed to remain at room temp for 2 hr and finally heated at 100° for 1 hr. On cooling, the ketone separated out as a dark oil. It was extracted

with ether and the ether solution washed with aqueous bicarbonate. Subsequent extraction with aqueous sodium carbonate (10%) and acidification of the extract yielded the ketone as an almost colourless solid which crystallized from benzene–light petroleum mixture as long prismatic needles (5 g) m.p. 101–102°. It gave a reddish violet colour with alcoholic ferric chloride (Found: C, 66·1; H, 5·4; $C_{16}H_{16}O_5$ requires: C, 66·6; H, 5·5%.).

7-Hydroxy-5,8-dimethoxyisoflavone (XVI)

XV (2 g) was cyclized using methyl formate (40 cc) and powdered sodium (1 g); the *isoflavone* crystallized from ethanol as colourless prisms (0·2 g) m.p. 254–256° with sintering at 240°. It was soluble in aqueous sodium hydroxide and sodium carbonate but gave no colour with ferric chloride (Found: C, 68·7; H, 4·7; $C_{17}H_{14}O_5$ requires: C, 68·4; H, 4·6%).

5,7-Dihydroxy-8-methoxyisoflavone (XVII)

(a) 7-Hydroxy-5,8-dimethoxyisoflavone (0·5 g) in dry nitrobenzene (50 cc) was treated with anhydrous aluminium chloride (0·45 g, 2 mole), and heated (water-bath) for 1 hr and nitrobenzene removed by steam distillation. The residue was treated with dilute HCl and heated (water-bath) for ½ hr. After cooling the isoflavone separated as a solid which crystallized from ethyl acetate–light petroleum mixture as colourless prisms (0·2 g) m.p. 174–176°. It gave a reddish violet colour with alcoholic ferric chloride which changed to green with excess of the reagent (Found: C, 67·5; H, 4·4; $C_{16}H_{12}O_5$ requires: C, 67·6; H, 4·2%).

(b) The same product (0·1 g) was obtained by refluxing XVI (0·2 g) in dioxane (5 cc) with conc HCl (2 cc) for 4 hr, removing dioxane under reduced pressure, adding water and crystallizing the solid.

5,7-Dihydroxy-6-methoxyisoflavone (XIV)

XVII (0·3 g) was isomerized with alcoholic potash (30 cc, 2%), and the isomeric *isoflavone* crystallized from ethyl acetate–light petroleum mixture as colourless long prismatic needles (0·15 g) m.p. and mixed m.p. 154–156°.

We convey thanks to Prof. F. E. King for a sample of natural muningin.