SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part XLII. A New Synthesis of 5 : 6 : 7-Trihydroxy Isoflavone Derivatives

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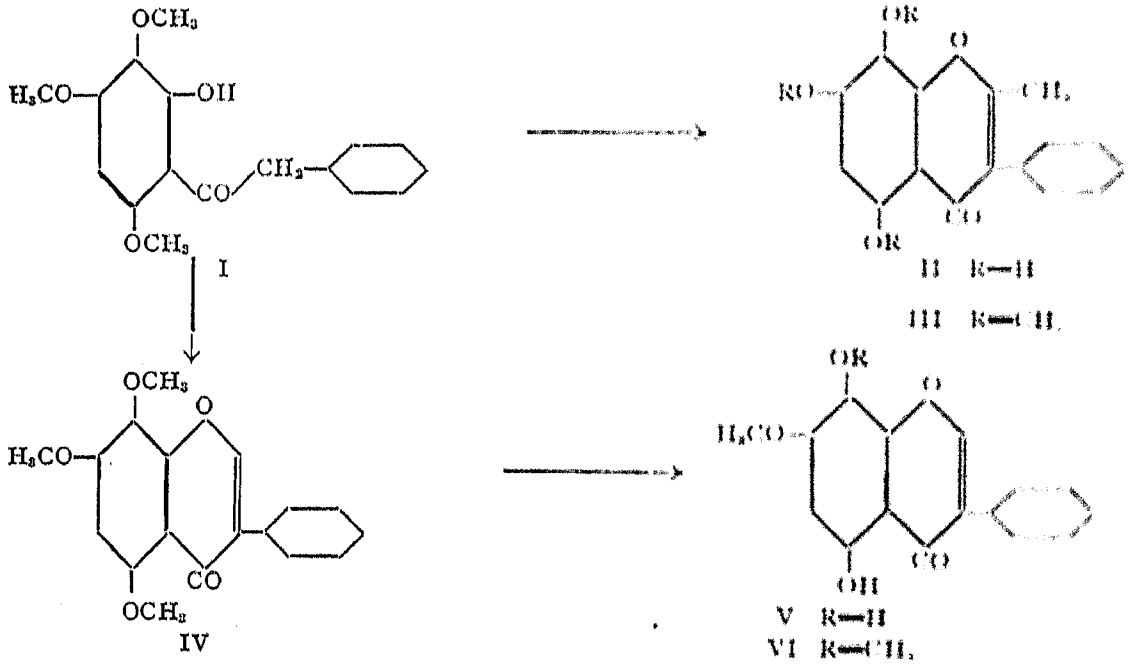
In an earlier paper[1] a convenient method of preparing 5 : 6 : 7-trihydroxy isoflavones starting from antiarol was described. Meanwhile experiments had been in progress in this laboratory to find out alternative methods for their synthesis. The methods known to be successful in the case of flavones were first examined. As already pointed out the nuclear oxidation of 2-hydroxy-4 : 6-dimethoxy-phenyl benzyl ketone did not proceed satisfactorily.[2] This may partly be attributed to the very low solubility of the ketone in alkali but even the addition of pyridine did not give a satisfactory yield. The second convenient method of preparation is the conversion of the more readily available 5 : 7 : 8-trihydroxy (methoxy) compounds into the corresponding 5 : 6 : 7-trihydroxy compounds by means of boiling hydriodic acid. This has been very successful in the case of flavones and has been used by Rao, Seshadri and Viswanadham[3] as preparative method; but this isomeric change does not take place under the same conditions in the case of flavonols and isoflavones[2] and therefore is not available for the present purpose.

A new route for the conversion of 5 : 7 : 8-trihydroxy (methoxy) isoflavones into the corresponding 5 : 6 : 7-trihydroxy (methoxy) compounds has now been examined. Earlier tectorigenin dimethyl ether was prepared by Shriner and Stephenson[4] by using 2 : 6-dihydroxy-3 : 4 : 4′-trimethoxy-phenyl-benzyl ketone as the intermediate. The synthesis of the intermediate was rather tedious and involved a number of difficult steps. Attempts have now been made to prepare this type of ketone in a different way starting from the easily available 5 : 7 : 8-trihydroxy (methoxy) isoflavones by alkali fission. Thus this constitutes essentially a method of conversion of one isoflavone into its isomer.

2-Methyl-5 : 7 : 8-trihydroxy isoflavone (II) was originally made by the nuclear oxidation of 2-methyl 5 : 7-dihydroxy isoflavone.[2] It could be subjected to partial methylation to yield the 7 : 8-dimethyl ether (XVI). Owing

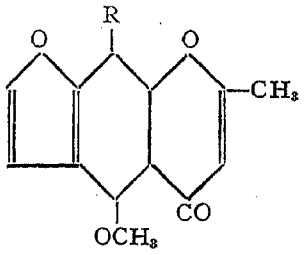
to poor yields in the nuclear oxidation the method is not convenient. In the second method 1:2:3:5-tetramethoxy benzene is condensed with phenyl-acetyl chloride to yield 2-hydroxy-3:4:6-trimethoxy-phenyl-benzyl ketone (I). On vigorous acetylation the 2-methyl isoflavone (III) is obtained. Here also the yields are comparatively poor and the methoxy isoflavone being low melting does not easily crystallise. The 5:7:8-trimethoxy isoflavone (IV) has also been obtained directly from the ketone (I) by the action of sodium and ethyl formate. The overall yields are better in this case and hence it has been prepared in larger quantities for detailed study.



To obtain 5-hydroxy-7:8-dimethoxy isoflavone (VI) from the 5:7:8-trimethoxy compound (IV) two methods could be used. In the first one the trimethoxy isoflavone (IV) is subjected to controlled demethylation with hydriodic acid when it yields 7-methoxy-5:8-dihydroxy isoflavone[5] (V) and by partial methylation the required dimethyl ether (VI) is obtained. It may be mentioned that the use of hydriodic acid under controlled conditions has been studied in great detail and a number of 7-methyl ethers of isoflavones prepared.[6]

The same compound (VI) could be prepared by a simpler method which is based on the observation that concentrated hydrochloric acid brings about easy demethylation of the 5-methoxy group alone yielding the product in an almost quantitative yield. The reagent has been used earlier for the demethylation of the 5-methoxy group in visnagin[7] (VII) and kellin[8] (VIII) and it does not cause isomeric change. In the field of isoflavones the reagent

was first used by Dhar, Narasimhachari and Seshadri.[9] This method is definitely better and simpler than the two stage process described earlier and yields are very good.

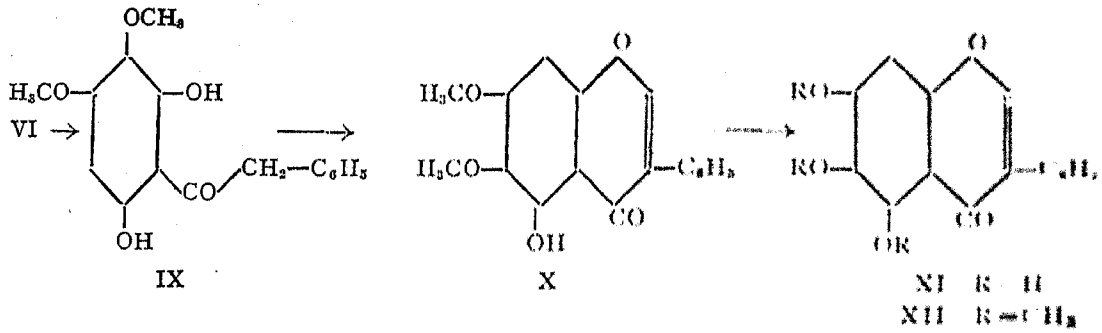


VII R=H
VIII R=OCH_3

The isoflavone (VI) is then subjected to fission with hot 8% absolute alcoholic potash. The resulting 2: 6-dihydroxy-3: 4-dimethoxy-phenyl-benzyl ketone (IX) is best purified by dissolving in aqueous sodium carbonate and reprecipitating with acid. When it is condensed with ethyl formate and sodium at 0° the resulting compound gives all the reactions characteristic of 5-hydroxy isoflavone derivatives. But it is different from 5-hydroxy-7: 8-dimethoxy isoflavone (VI) in melting point and colour reactions and therefore should be 5-hydroxy-6: 7-dimethoxy isoflavone (X). On complete demethylation with hydriodic acid or anhydrous aluminium chloride in benzene solution it gives a trihydroxy compound [5: 6: 7-trihydroxy isoflavone (XI)], which does not differ markedly from its 5: 7: 8-isomer in reactions. But the mixed melting point shows marked depression and the derivatives differ markedly.

The differences are brought out clearly in the following table:—

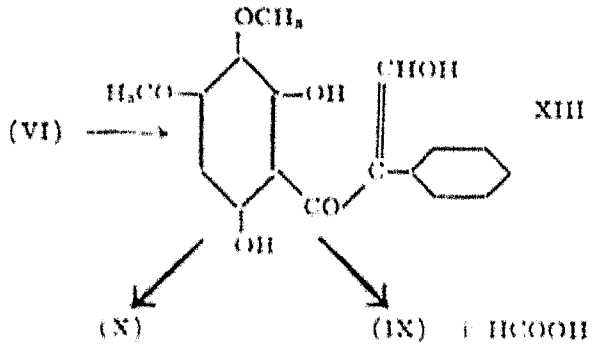
S. No.	Compound	5 : 7 : 8–substituted isoflavone derivative	5 : 6 : 7–substituted isoflavone derivative
1	Trihydroxy compound— (*a*) melting point (*b*) colour with ferric chloride	 280–282° green changing to brown	 282–283° (decomp.) olive green changing to deep brown
2	Triacetyl derivative (melting point)	206–208°	185–186°
3	Trimethyl derivative (melting point)	150–151°	165–166°
4	5–Hydroxy dimethyl ether (*a*) melting point (*b*) colour with ferric chloride	 159–160° green	 203–205° bluish violet
5	5–Acetoxy-dimethyl ether (melting point)	143–144°	121–123°



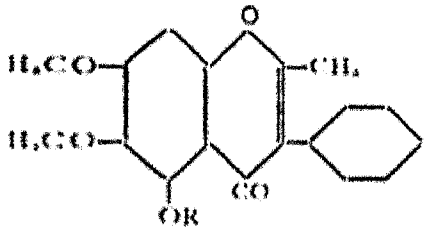
IX X XI R = H XII R = CH_3

An interesting observation has been made in the course of the fission of 5-hydroxy-7: 8-dimethoxy isoflavone (VI), which indicated the presence of a compound sparingly soluble in aqueous alkali. It was actually this observation that led to the purification of 2: 6-dihydroxy-3: 4-dimethoxy-phenyl-benzyl ketone (IX) with aqueous sodium carbonate. The carbonate insoluble compound melted at 203–05°, gave a bluish violet colour with ferric chloride, was very sparingly soluble in aqueous alkali and was identical with 5-hydroxy-6: 7-dimethoxy isoflavone (X); a mixed melting point with an authentic sample of this structure described earlier showed no depression. A possible explanation for this peculiar and novel result suggests itself from the recent work of Rajagopalan, Narasimhachari and Seshadri[10] on the use of methyl formate in the isoflavone condensation. They suggested that the ω-formyl or hydroxymethylene (see XIII) derivative of a phenyl-benzyl ketone which may be the initial product of the condensation, may undergo change in two directions; one involving simple isomeric change leads to a 2-hydroxy isoflavanone while the other involving a dehydration leads to the isoflavone (X) itself. They considered that on the alkalinity of the medium would depend the course of the reaction; a higher alkalinity favours dehydration, while in the absence of it isomeric ring closure takes place.

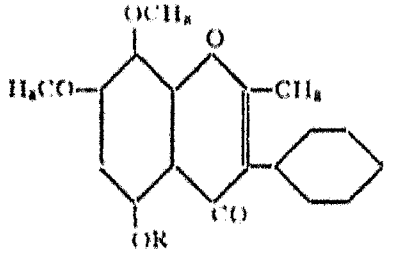
In the present case the alkali hydrolysis of the isoflavone (VI) leads to the opening of the pyrone ring, forming a hydroxymethylene compound (XIII) which then undergoes further fission yielding the phenyl-benzyl ketone (IX) and formic acid. A small portion of (XIII) seems to undergo ring closure instead of fission and as in several similar cases the ring closure from this open structure involves the hydroxyl which is para to a methoxyl thus giving rise to the isoflavone (X). This, therefore, constitutes a direct isomeric change of the 5: 7: 8-hydroxy (methoxy) type to the 5: 6: 7-hydroxy (methoxy) type in isoflavones under alkaline conditions. The yield of the isomeric compound is however low and the reaction is not therefore of preparative value. But the change effected in two stages, the ketone forming the intermediate stage is definitely useful.



With acetic anhydride and sodium acetate the 2:6-dihydroxy-3:4-dimethoxy-phenyl-benzyl ketone (IX) undergoes isoflavone ring closure to yield 2-methyl-5-acetoxy-6:7-dimethoxy isoflavone (XV) which on deacetylation gave 2-methyl-5-hydroxy-6:7-dimethoxy isoflavone (XIV). This and its acetate are different from 2-methyl-5-hydroxy-7:8-dimethoxy isoflavone (XVI) and its acetate (XVII). Its identity is confirmed by a comparison with a sample of 2-methyl-5-hydroxy-6:7-dimethoxy isoflavone prepared by the partial demethylation of 2-methyl-5:6:7-trimethoxy isoflavone described by Krishnamurty and Seshadri.[1]



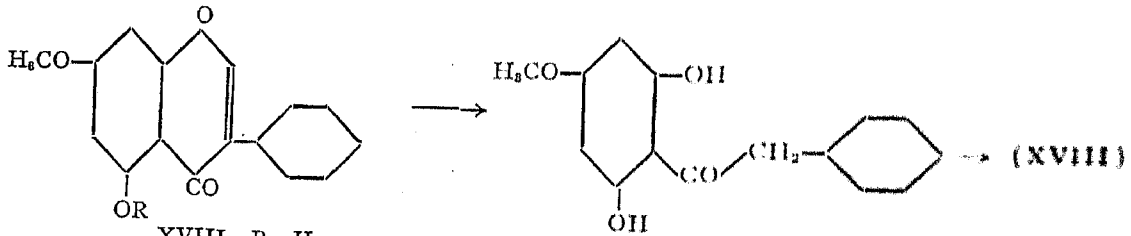
XIV R=H
XV R=CH₃CO



XVI R=H
XVII R=CH₃CO

As an exploratory study during the earlier stages of this work two points had to be considered. Firstly not much work was known on the controlled fission of hydroxy isoflavones to yield the corresponding phenyl-benzyl ketones. Hence it was necessary to study the simplest example in order to get a preliminary idea of the course of the reaction, the nature of the products and their yields. The easily available 5-hydroxy-7-methoxy isoflavone (XVIII) was chosen for this study and it was prepared from 5:7-dimethoxy isoflavone (XIX) by demethylation using hydriodic acid at 110° and also boiling concentrated hydrochloric acid. On fission with 8% absolute alcoholic potassium hydroxide and purifying the fission product using aqueous sodium carbonate 2:6-dihydroxy-4-methoxy-phenyl-benzyl ketone (XX) was obtained. The analytical values and the reactions of the ketone agreed with its expected structure. Its constitution was further confirmed by reconversion into the original 5-hydroxy-7-methoxy-isoflavone (XVIII).

Secondly, the use of polyhydroxy ketones for isoflavone condensations using the ethyl formate method has not been commonly adopted. The dihydroxy ketone (XX) gives a satisfactory yield of 5-hydroxy-7-methoxy isoflavone indicating that 2: 6-dihydroxy ketones are in general suitable for this condensation. This is further supported by the more complex example given earlier.



XVIII R=H
XIX R=CH_3

XX

After the work described in this paper was completed we read the communication of Baker *et al.*[11] in which they reported the isomerisation of 5: 7: 8-trihydroxy isoflavones when boiled for eight hours with hydrobromic and acetic acids. In their earlier work Narasimhachari, Row and Seshadri[8] reported the absence of isomeric change when 5: 7: 8-trimethoxy isoflavones were demethylated with hydriodic acid and supported their conclusion by remethylation to the original isoflavone trimethyl ethers. They did not however possess authentic samples of 5: 6 : 7-trihydroxy derivatives for comparison. As the result of the present work these have become available and the earlier observations of Narasimhachari, Row and Seshadri,[8] are found to be correct. Baker *et al.*[11] however report that the conditions of the reaction are the deciding factor, whether or not rearrangement occurs and the details are not yet fully available.

In the same communication Baker *et al.*, report differences in the ring closure using different reagents. Ethyl formate is reported to give the 5: 6: 7-isomer from 2: 6-dihydroxy-4: 5: 4′-trimethoxy-phenyl-benzyl ketone whereas ethyl oxalyl chloride yields the 5: 7: 8-isomer from 2: 4: 6: 4′-tetrahydroxy-5-methoxy ketone. The results recorded in the present paper confirm their observation regarding the ethyl formate condensation.

EXPERIMENTAL

2: 6-*Dihydroxy-4-methoxy-phenyl-benzyl ketone* (*XX*)

5-Hydroxy-7-methoxy isoflavone (XVIII) required for this preparation was made from 5: 7-dimethoxy isoflavone (XIX) as follows: To 5: 7-dimethoxy isoflavone (1 g.) was added concentrated hydrochloric acid (15 c.c.) and mixture boiled under reflux; the isoflavone quickly dissolved yielding a yellow solution and a sticky semi-solid separated in the course of half an

hour. The mixture was then diluted with water (50 c.c.) and cooled well. The aqueous solution was decanted off and the sticky solid treated with a little alcohol (5 c.c.) when it turned rapidly into a crisp solid. It crystallised from ethyl acetate as stout rectangular prisms melting 140–41°. Yield 0·9 g. A mixed melting point with an authentic sample prepared by the method of Aghoramurthy *et al.*[6] was undepressed.

5-Hydroxy-7-methoxy isoflavone (1 g.) was dissolved in 8% absolute alcoholic potassium hydroxide (15 c.c.) and the solution refluxed for four hours. As much alcohol as possible was then removed under reduced pressure by heating on a boiling water-bath. The residue was dissolved in water and the solution acidified with hydrochloric acid. The product was directly taken in ether and the ether solution extracted thrice with 10 c.c. portions of 5% aqueous sodium carbonate. On acidifying the combined carbonate extract the ketone was obtained which crystallised as pale brown prisms from dilute methanol and melted at 142–43°. It gave a violet colour with ferric chloride. Yield 0·3 g. (Found: C, 69·2; H, 5·7. $C_{16}H_{14}O_4$ requires C, 69·7; H, 5·4%).

Conversion into 5-hydroxy-7-methoxy isoflavone (XVIII)

The above ketone (0·6 g.) was dissolved in ethyl formate (5 c.c.) and cooled in ice. Powdered sodium (0·5 g.) cooled in ice, was added to the above solution in small quantities at a time. The mixture was allowed to stand in a refrigerator for 48 hours. Ice pieces were added to it and the excess of ethyl formate was removed under reduced pressure. On cooling the oily liquid initially formed soon solidified. It crystallised from ethyl acetate as stout rectangular prisms melting at 140–41°. Yield 0·3 g. The colour reactions agreed with those of the authentic sample of 5-hydroxy-7-methoxy isoflavone and the mixed melting point was undepressed.

5-Hydroxy-7 : 8-dimethoxy isoflavone (VI)

This was first made by following the method of Narasimhachari, Row and Seshadri[2] employing partial methylation of 5: 7: 8-trihydroxy isoflavone.

It has now been obtained by the partial demethylation of 5: 7: 8-trimethoxy isoflavone (1 g.) just in the same way as with 5: 7-dimethoxy isoflavone using concentrated hydrochloric acid as demethylating agent. It crystallised from alcohol as aggregates of stout rhombic prisms melting at 159–60°. Yield 0·8 g. It was identical with the product described earlier.[2] 5-Acetoxy-7: 8-dimethoxy isoflavone obtained by heating the 5-hydroxy derivative with acetic anhydride and pyridine crystallised from ethyl acetate as colourless long rectangular rods and prisms melting at 143–44°. (Found: C, 66·5; H, 4·5. $C_{19}H_{16}O_6$ requires C, 67·0; H, 4·7%.)

2-Methyl-5-hydroxy-7 : 8-dimethoxy isoflavone (XVI)

(*a*) *Partial methylation.*—2-Methyl-5 : 7 : 8-trihydroxy isoflavone[a] (II) (0·6 g.) was refluxed in dry acetone (70 c.c.) with dimethyl sulphate (0·45 c.c.) and anhydrous potassium carbonate (2 g.) for six hours. The potassium salts were filtered off and washed with hot acetone. On distilling off acetone from the filtrate a yellow sticky solid was obtained. It did not solidify even on long keeping. It was therefore converted into its acetate by refluxing with acetic anhydride and pyridine and then pouring on ice. The solid crystallised from alcohol as colourless narrow rectangular plates melting at 207–208°. (Found: C, 66·4; H, 4·8. $C_{20}H_{18}O_8\ \frac{1}{2}H_2O$ requires C, 66·1; H, 5·2%.) The acetate was deacetylated by heating it with alcoholic hydrochloric acid (1 : 1; 5 c.c.) for 10 minutes. On diluting with water a sticky mass separated, the mother liquor was decanted off and the residue dissolved in methyl alcohol (2 c.c.). On allowing it to stand for a number of days in the refrigerator pale yellow tiny prisms having a melting point of 168–69° separated. (Found: C, 69·7; H, 5·1. $C_{18}H_{16}O_6$ requires C, 69·2; H, 5·1%).

(*b*) *Partial demethylation.*—2-Methyl-5 : 7 : 8-trimethoxy isoflavone required for this experiment was obtained by heating 2-hydroxy-3 : 4 : 6-trimethoxyphenyl-benzyl ketone (6·8 g.) with fused sodium acetate (10 g.) and acetic anhydride (40 c.c.) at 170–80° for sixteen hours. After treatment with ice the solid product crystallised from alcohol as transparent stout rectangular prismatic rods melting at 93–94°. Yield 1·8 g.

Starting with 2-methyl-5 : 7 : 8-trimethoxy isoflavone (0·8 g.) the partial demethylation was carried out just in the same way as with 5 : 7-dimethoxy isoflavone using concentrated hydrochloric acid as demethylating agent. Due to difficulty in crystallisation the crude product was directly converted into the acetate which on crystallisation from alcohol separated as colourless narrow rectangular plates melting at 207–08°. Mixed melting point with the above sample of 5-acetoxy-7 : 8-dimethoxy-2-methyl isoflavone was undepressed.

2 : 6-Dihydroxy-3 : 4-dimethoxy-phenyl-benzyl ketone (IX)

(*a*) *By the fission of 5-hydroxy-7 : 8-dimethoxy isoflavone (VI).*—5-Hydroxy-7 : 8-dimethoxy isoflavone (0·8 g.) was dissolved in 8% absolute alcoholic potassium hydroxide (20 c.c.) and the solution refluxed for four hours. As much alcohol as possible was then removed under reduced pressure by heating on a boiling water-bath. Water (15 c.c.) was added when a part of the solid dissolved and a part remained undissolved. The whole

of the mixture was acidified with hydrochloric acid and then directly taken up in ether. The ether solution was extracted thrice with 10 c.c. portions of 5% aqueous sodium carbonate. On acidifying the combined carbonate extract the ketone was obtained which separated as yellowish spear-head shaped crystals from alcohol and melted at 161–62°. Yield 0·4 g. (Found: C, 66·6; H, 5·5. $C_{18}H_{16}O_6$ requires C, 66·7; H, 5·5%). It gave a red colour with alcoholic ferric chloride. The ether solution left after the extraction with carbonate was washed with water and dried over anhydrous sodium sulphate. On distilling off ether, a colourless solid was left behind. It was crystallised from excess of alcohol when a small quantity of a sparingly soluble product separated (80 mg.) as colourless rectangular plates and tablets melting at 203–05°. It gave a bluish violet colour with ferric chloride and was sparingly soluble in aqueous sodium hydroxide. It agreed in its properties with 5-hydroxy-6: 7-dimethoxy isoflavone described later and a mixed melting point with that sample was undepressed.

(*b*) *By fission of 2-methyl-5-hydroxy-7: 8-dimethoxy isoflavone* (XVI).—2-Methyl-5-hydroxy-7: 8-dimethoxy isoflavone (0·5 g.) was heated with 10 c.c. of 8% absolute alcoholic potassium hydroxide for four hours and the product worked up as in the previous case. The crystallised product was identical with the ketone sample described above and the mixed melting point was undepressed. Yield 0·2 g.

5-Hydroxy-6: 7-dimethoxy isoflavone (*X*)

Pulverised sodium (0·5 g.) and a solution of 2: 6-dihydroxy-3: 4-dimethoxy-phenyl-benzyl ketone (0·5 g.) in dry ethyl formate (5 c.c.) were employed. The product crystallised from ethyl acetate as colourless rectangular plates and tablets melting at 203–05°. Yield 0·3 g. (Found: C, 68·4; H, 5·1; $C_{17}H_{14}O_6$ requires C, 68·5; H, 4·7%). It was found to be different from 5-hydroxy-7: 8-dimethoxy isoflavone in colour reactions and the mixed melting point was depressed considerably. The colour with alcoholic ferric chloride was bluish violet.

Using acetic anhydride and pyridine 5-acetoxy-6: 7-dimethoxy isoflavone was prepared and it crystallised from alcohol as colourless aggregates of long needles melting at 121–23° (Found: C, 67·2; H, 4·9; $C_{19}H_{16}O_6$ requires C, 67·0; H, 4·7%).

5: 6: 7-*Trimethoxy isoflavone* (*XII*)

5-Hydroxy-6: 7-dimethoxy isoflavone (0·3 g.) was refluxed in dry acetone (70 c.c.) with dimethyl sulphate (0·15 c.c.) and anhydrous potassium carbonate (1 g.) for sixteen hours. The potassium salts were filtered off and

washed with hot acetone. On distilling off the acetone from the filtrt e a colourless solid was obtained. Crystallisation from alcohol yielded the methyl ether as colourless rhombic prisms melting at 165–66°. Yield 0·15 g. (Found: C, 65·8; H, 5·8; $C_{18}H_{16}O_5$ requires C, 65·5; H, 5·4%). It did not dissolve in cold aqueous sodium hydroxide and did not give any colour with ferric chloride. The mixed melting point with the isomeric 5:7:8-trimethoxy isoflavone is considerably depressed.

5:6:7-*Trihydroxy isoflavone (XI)*

An acetic anhydride solution of 5-hydroxy-6:7-dimethoxy isoflavone (0·3 g. in 2 c.c.) was treated with cooling with hydriodic acid (sp. gr. 1·7, 6 c.c.) and the mixture heated on an oil-bath at 140–45° for two hours. It was then cooled and diluted with sulphurous acid. The bright yellow solid that separated was filtered, washed with water and crystallised from alcohol when it separated as yellow micaceous aggregates of thin rectangular plates melting at 282–83° (decomp.). Yield 0·15 g. (Found: C, 66·1; H, 4·0; $C_{15}H_{10}O_5$ requires C, 66·6; H, 3·7%). With ferric chloride it gave an olive green colour which changed to deep brown when excess was added. With sodium hydroxide solution it gave orange red colour which changed to brownish red, violet and finally blue.

5:6:7-Triacetoxy isoflavone was made by the acetic anhydride-pyridine method. It crystallised from alcohol as colourless narrow rectangular plates melting at 185–86°. (Found: C, 63·3; H, 4·0; $C_{21}H_{16}O_8$ requires C, 63·6; H, 4·0%); see Karmarkar *et al.*[12]

2-*Methyl*-5-*hydroxy*-6:7-*dimethoxy isoflavone (XIV)*

(1) 2:6-Dihydroxy-3:4-dimethoxy-phenyl-benzyl ketone (0·5 g.) was mixed with fused sodium acetate (0·5 g.) and heated with acetic anhydride (5 c.c.) under reflux in an oil-bath at a temperature of 170–80° for twelve hours. The contents were cooled and poured into crushed ice (30 g.) and left overnight. The slightly brownish product was filtered and crystallised from alcohol when 2-methyl-5-acetoxy-6:7-dimethoxy isoflavone separated as colourless rhombohedral prisms melting at 193–94°, yield 0·2 g. (Found: C, 67·5; H, 5·1; $C_{20}H_{18}O_6$ requires C, 67·8; H, 5·1%).

2-Methyl-5-acetoxy-6:7-dimethoxy isoflavone (0·1 g.) was boiled with 10 c.c. of 4% sodium hydroxide for 10 minutes. The solution was filtered hot to remove undissolved impurities, cooled well and acidified with hydrochloric acid. The product was taken up in ether and after drying the ether solution over anhydrous sodium sulphate the isoflavone was recovered by evaporation. It crystallised from alcohol as aggregates of colurless stout

prismatic rods melting at 145–46°. It gave blusih violet colour with alcoholic ferric chloride. It was identical with 2-methyl-5-hy lroxy-6: 7-dimethoxy isoflavone described below.

(2) 2-Methyl-5: 6: 7-trimethoxy isoflavone[1] (50 mg.) was refluxed with concentrated hydrochloric acid (2 c.c.) for fifteen minutes. It was then diluted with water (10 c.c.) and the colourless solid that separated was filtered and washed with water. When crystallised from alcohol it separated as colourless stout prismatic rods melting at 145–46°. It gave a bluish violet colour with alcoholic ferric chloride. (Found: C, 69·6; H, 5·4; $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1%).

Summary

Using the more easily accessible 5: 7: 8-trihydroxy derivatives of isoflavones a convenient method has been worked out for the synthesis of 5: 6: 7-trihydroxy derivatives. It consists in the alkali fission of 5-hydroxy-7: 8-dimethoxy isoflavone and its 2-methyl derivative to yield 2: 6-dihydroxy-3: 4-dimethoxy-phenyl-benzyl ketone. This ketone on treatment with ethyl formate and sodium yields 5-hydroxy-6: 7-dimethoxy isoflavone. Vigorous acetylation of the ketone using acetic anhydride and sodium acetate yields 2-methyl-5-hydroxy-6: 7-dimethoxy isoflavone which is compared with an authentic sample prepared by an independent method. 5-Hydroxy-7: 8-dimethoxy isoflavone yields a small quantity of 5-hydroxy 6: 7-dimethoxy isoflavone during alkali fission.

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