SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part XLI. Constitution of Tectorigenin and Synthesis of Tectorigenin Triethyl Ether

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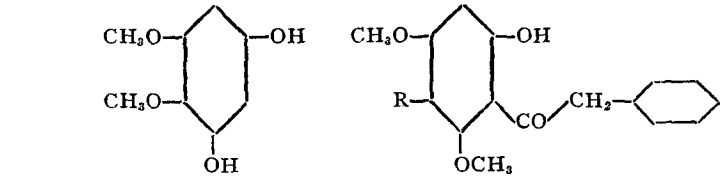
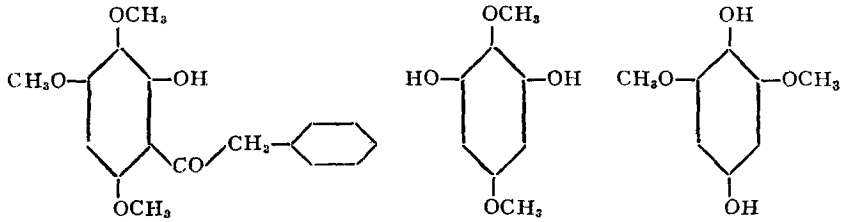
COMPARED with the flavones and flavonols there are only a few members of the isoflavone group having more than two hydroxyl groups in the condensed benzene ring. However, the number seems to be increasing; irigenin was the earliest to be discovered, later on came tectorigenin and more recently muningin. It is possible that others will be discovered in future. In regard to their synthesis it is comparatively easy to prepare members of the 5:7:8-trihydroxy series, the simplest method being the nuclear oxidation of 5:7-dihydroxy isoflavones.[1] The preparation of the isomeric 5:6:7-hydroxy or methoxy isoflavones has been found to be difficult. The only method so far employed uses 4:5-dimethoxy resorcinol[2] (I) which is rather difficult to prepare. Further this method is not suitable for all purposes. Consequently a search was necessary for more convenient routes of synthesis. At first attempts were made to subject 2-hydroxy-4:6-dimethoxy phenyl benzyl ketone (II) to nuclear oxidation with persulphate to yield 2:5-dihydroxy-4:6-dimethoxy phenyl benzyl ketone (III) which could be cyclised to the required isoflavone. But the oxidation was unsuccessful. 1:2:3:5-Tetramethoxy benzene yields always 2-hydroxy-3:4:6-trimethoxy phenyl benzyl ketone (IV) when subjected to Friedel and Craft's reaction and hence this was also unsuitable for the purpose of making the 5:6:7-hydroxy isoflavones. Similar was the case wtih 2:5-dimethoxy resorcinol (V). Though 2:6-dimethoxy quinol (VI) has the required structure and yields the corresponding aldehyde readily it has been found to be unreactive in the Hoesch reaction. Even in the Friedel and Craft's reaction lack of reactivity is exhibited. Very recently however, Karmarkar *et al.*[14] have shown that it can react with the boron trifluoride complex of phenyl acetic acid to yield the corresponding ketone.

In the course of a systematic study of other starting materials, antiarol (VII) has now been found to be quite satisfactory. It has been known to yield the corresponding aldehyde by the Gattermann reaction readily, but

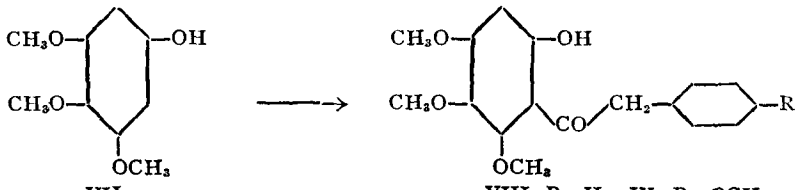


I II. R=H; III. R=OH

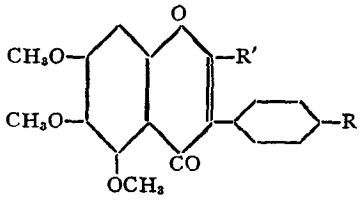


IV V VI

is inert in the Hoesch reaction. It is however, sufficiently reactive in the Friedel and Craft's reaction with phenyl acetyl chloride and its *p*-methoxy derivative.[3] Thus antiarol has provided a very suitable starting material for the synthesis of derivatives belonging to the 5:6:7-hydroxy type (*i.e.*, irigenol series). The steps in the synthesis are indicated by the following formulæ:



VII VIII. R=H; IX. R=OCH_3

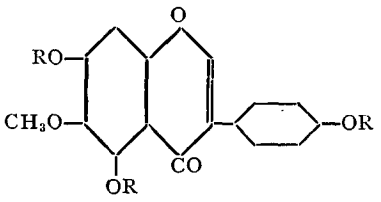


X. R=H; R'=CH_3
XI. R=OCH_3; R'=H

Constitution of tectorigenin

Tectorigenin, the aglucone of tectoridin, was first isolated by Shibata[4] from the rhizomes of Iris tectorum. It was later found to be present in *Pardanthus chinensis* (*Belamcanda chinensis*) also.[5] Shibata made a detailed study of its reactions. He found that it had three hydroxyl groups capable of forming a triacetate and tribenzoate quite readily. But it formed only a dimethyl ether, the third hydroxyl being resistant. On boiling with alkali

it gave rise to formic acid, iretol and *p*-hydroxy phenyl acetic acid. The correct constitution was however given by Asahina and co-workers.[6] They determined its molecular formula as $C_{16}H_{12}O_6$. Based on the similarity between tectorigenin and irigenin and on a study of the absorption spectrum of tectorigenin they suggested for it the structure of 6-methoxy-5:7:4′-trihydroxy isoflavone which is now accepted (XII).



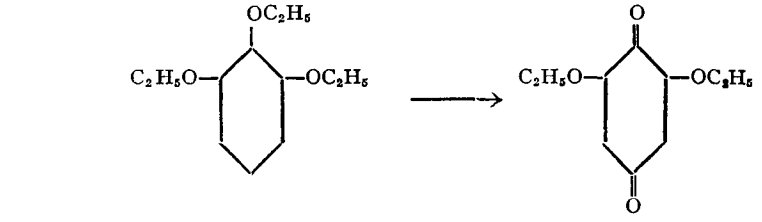
XII. R=H XVII, R=C_2H_5

Synthetic support for this structure was first afforded by the work of Shriner and Stephenson[2] who, as already mentioned, started from 4:5-dimethoxy resorcinol and obtained the 7:4′-dimethyl ether of tectorigenin which is also the product of methylation of tectorigenin. During the course of the present work tectorigenin from *Iris tectorum* and *Belamcanda chinensis* has been fully methylated to yield the trimethyl ether (XI) which has also been obtained synthetically starting from antiarol (VII).

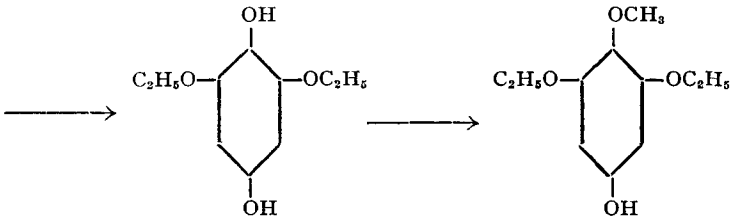
The synthetic work mentioned in the previous para confirms that tectorigenin is a monomethyl ether of 5:6:7:4′-tetrahydroxy isoflavone. The location of the methoxyl group in the 6-position was originally based on the formation of iretol as one of the degradation products. To confirm this point tectorigenin has now been completely ethylated and the constitution of the triethyl ether established by synthesis using unambiguous methods. The new method of synthesis described earlier in this paper has been found to be quite suitable for this purpose. 3:5-diethoxy-4-methoxy phenol is used as the starting material. It is obtained from pyrogallol by the following series of reactions. Pyrogallol is first ethylated to the triethyl ether (XIII) with ethyl iodide in dry acetone solution in the presence of potassium carbonate; oxidation with nitric acid in alcoholic solution yields the diethoxy quinone (XIV). The quinone is reduced to the quinol (XV) by means of stannous chloride in the presence of hydrochloric acid. Subsequent partial methylation employing the method of Chapman, Perkin and Robinson[7] yields the desired diethoxy-monomethoxy phenol (XVI).

p-Ethoxy phenyl acetic acid was earlier obtained by the ethylation of *p*-hydroxy phenyl acetic acid.[8] It has now been obtained from *p*-ethoxy phenyl pyruvic acid. This is converted into the oxime. The oxime on

treatment with acetic anhydride yields the nitrile which is hydrolysed to the acid. Condensation of 3 : 5-diethoxy-4-methoxy phenol and *p*-ethoxy phenyl



XIII XIV



XV XVI

acetyl chloride in cold ether solution in the presence of anhydrous aluminium chloride yields a ketone which does not solidify. Hence it is characterised as the dinitrophenyl hydrazone. Cyclisation with ethyl formate affords 5 : 7 : 4′-triethoxy-6-methoxy isoflavone (XVII). For purpose of comparison an authentic sample of the triethyl ether of tectorigenin has been made from tectorigenin isolated from *Iris tectorum* and *Belamcanda chinensis*.[9] The mixed m.p. of this compound with the synthetic sample was undepressed.

Experimental

2-Hydroxy-4 : 5 : 6-trimethoxy phenyl benzyl ketone (VIII)

Antiarol required for this experiment was prepared by the method of Chapman, Perkin and Robinson.[7]

Anhydrous aluminium chloride (5 g.) was dissolved in dry ether (50 c.c.) with cooling and to the solution was added antiarol (3 g.) in dry ether (50 c.c.). The mixture was then treated with phenyl acetyl chloride (3 c.c.) while cooling in ice, the reaction mixture was shaken occasionally for about two hours and then left at room temperature for 12 hours. Ether was removed on a warm water-bath, the remaining organo-aluminium complex first treated with ice and hydrochloric acid and subsequently heated on the water-bath to complete the hydrolysis. The solution was then extracted with ether, the ether extract washed with sodium bicarbonate solution (5%) and then with water and dried over anhydrous sodium sulphate. Evaporation of the dried

ether extract left a viscous mass which solidified on keeping. It crystallised from methyl alcohol in the form of colourless thin plates melting at 64°. Yield 2·2 g. It gave a brown colour with ferric chloride (Found: C, 67·8; H, 5·9. $C_{17}H_{18}O_5$ requires C, 67·6; H, 6·0%).

2-Methyl-5: 6: 7-trimethoxy isoflavone (X)

The above ketone (1·5 g.) was refluxed with acetic anhydride (20 c.c.) and freshly fused sodium acetate (6 g.) for 12 hours. The excess of acetic anhydride was then decomposed by adding alcohol. Next day the mixture was distilled to remove alcohol and ethyl acetate and the residue was taken up in ether. The ether extract was washed thrice with aqueous sodium hydroxide (5%) and then with water. After drying over magnesium sulphate, ether was removed by evaporation. The solid obtained crystallised from alcohol in the form of colourless prisms melting at 154°. Yield 0·6 g. It was insoluble in aqueous sodium hydroxide and gave no colour with alcoholic ferric chloride (Found: C, 70·3; H, 5·6; $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·5%).

2-Methyl-5: 6: 7-trihydroxy isoflavone

The trimethoxy isoflavone (0·8 g.) in acetic anhydride solution (10 c.c.) was treated with cooling with hydriodic acid (sp. gr. 1·7; 10 c.c.) and the mixture heated in an oil-bath at 140° for 3 hours. It was then cooled and diluted with sulphur dioxide water. The trihydroxy isoflavone was filtered, washed with water and crystallised from alcohol when it was obtained in the form of pale yellow rhombohedral crystals melting at 222°. Yield 0·5 g. It dissolved in aqueous sodium hydroxide forming an yellow solution and imparted a green colour to alcoholic ferric chloride (Found: C, 63·2; H, 4·9. $C_{16}H_{12}O_5$, H_2O requires C, 63·6; H, 4·6%).

The triacetate of the isoflavone was obtained by boiling with acetic anhydride and freshly fused sodium acetate. It crystallised from alcohol in the form of colourless plates melting at 205°.

2-Hydroxy-4: 5: 6-trimethoxy phenyl p-methoxy benzyl ketone (IX)

p-Methoxy phenyl acetyl chloride (1 c.c.) and antiarol (1·2 g.) were condensed in the presence of anhydrous aluminium chloride (1·2 g.) in dry ether solution (100 c.c.). The reaction was carried out as before and the product worked up. The ketone crystallised from alcohol in the form of colourless plates melting at 91–92°. Yield 0·6 g. It gave a brown colour with ferric chloride (Found: C, 65·3; H, 5·9. $C_{18}H_{20}O_6$ requires C, 65·1; H, 6·0%).

5:6:7:4′-*tetramethoxy isoflavone* (*XI*)

The above ketone (IX) (0·8 g.) dissolved in freshly distilled ethyl formate (20 c.c.) was added in portions of 3–4 c.c. at a time to pulverised sodium (0·5 g.) well cooled in ice. After shaking the mixture for about 2 hours it was left in the refrigerator for 48 hours. It was then added to crushed ice and the excess of ethyl formate was evaporated off. The solution was then extracted with ether. Evaporation of the dried ether extract left a solid which crystallised from methyl alcohol in the form of long rectangular plates melting at 176°. Yield 0·1 g. When mixed with a sample of the trimethyl ether of tectorigenin obtained from the natural source (see below) the m.p. was undepressed.

Trimethyl ether of tectorigenin

Tectorigenin (0·5 g.) was refluxed for 40 hours with dimethyl sulphate (0·6 c.c.) and anhydrous potassium carbonate (2 g.) in dry acetone solution (50 c.c.) and the mixture was worked up as usual. The trimethyl ether crystallised from methyl alcohol in the form of rectangular plates melting at 176°.

Pyrogallol triethyl ether (*XIII*)

Bayer and Co[10] obtained this compound by ethylation of pyrogallol with diazoethane. It has now been obtained by ethylation with ethyl iodide in dry acetone solution in the presence of potassium carbonate.

To a solution of pyrogallol (20 g.) in dry acetone (200 c.c.) ethyl iodide (55 c.c.) and anhydrous potassium carbonate (80 g.) were added and the mixture refluxed for 12 hours. The solution was filtered off while hot and the potassium carbonate washed twice with 50 c.c. portions of warm acetone. The solvent was distilled off and the residue was washed with sodium hydroxide to remove the mono and diethyl ethers. The triethyl ether slowly solidified on keeping it in the ice-chest and scratching with a glass rod, m.p. 39°. Yield 18 g.

2:6-*Diethoxy benzo-quinone* (*XIV*)

Spath and Wessely[11] obtained this quinone by the oxidation of phloroglucinol diethyl ether or of 4-methoxy-2:6-diethoxy-benzhydrol with chromic acid in glacial acetic acid medium; Pollak and Goldstein[12] employed pyrogallol triethyl ether and oxidised it with nitric acid in glacial acetic acid solution. It has now been prepared more conveniently by the oxidation of pyrogallol triethyl ether in alcohol solution with nitric acid (d, 1·19).

Nitric acid (50 c.c.; d, 1·19) was added to a solution of the triethyl ether 10 g.) in alcohol (50 c.c.) and the temperature was maintained below 50°.

After about 4 hours the nitro compound was filtered off and the filtrate diluted and kept overnight. The precipitated quinone was filtered and crystallised from alcohol when it was obtained as yellow rectangular rods and prisms melting at 127°. Yield 3·5 g.

2 : 6-*Diethoxy hydroquinone* (*XV*)

Stannous chloride (8 g.) was dissolved in a mixture of concentrated hydrochloric acid (20 c.c.) and water (10 c.c.) and the solution heated till it was clear. 2 : 6-diethoxy quinone (2 g.) was added to the solution and the heating continued for five more minutes. The solution was filtered and the filtrate cooled when it deposited crystals which were collected and crystallised from water containing a little hydrochloric acid. The quinol was obtained in the form of colourless plates melting at 170°. Yield 1·6 g. (Found: C, 57·9; H, 7·3. $C_{10}H_{14}O_4$, $\frac{1}{2}H_2O$ requires C, 58·0; H, 7·3%).

3 : 5-*Diethoxy*-4-*methoxy phenol* (*XVI*)

A solution of sodium hydroxide (4 g.) in water (30 c.c.) was added to 2 : 6-diethoxy quinol (6 g.) in a flask from which air was excluded by hydrogen. Methyl sulphate (3·8 c.c.) was then added in one portion with vigorous stirring which was continued for 10–15 minutes and then at intervals for about 1 hour. The alkaline solution was ether extracted to remove the completely methylated ether (2 g. was isolated) and then acidified. The 3 : 5-diethoxy-4-methoxy phenol was filtered off and crystallised from ten times its weight of water when it was obtained in the form of colourless elongated and stout rectangular prisms melting at 74°. Yield 2·5 g. (Found: C, 59·7; H, 7·2. $C_{11}H_{16}O_4$, $\frac{1}{2}H_2O$ requires C, 59·7; H, 7·7%).

2-*Hydroxy*-4 : 6-*diethoxy*-5-*methoxy-phenyl* p-*ethoxy benzyl ketone*

p-Ethoxy phenyl acetic acid (1·2 g.) was converted into the chloride using thionyl chloride. The product was directly condensed with 3 : 5-diethoxy-4-methoxy-phenol (1·2 g.) in cold ether in the presence of anhydrous aluminium chloride (2 g.). The reaction was carried out in the same way as in the preparation of (VIII). The ketone was obtained in the form of an oil and did not solidify. Hence it was characterised as the dinitrophenyl hydrazone which melted at 162° (Found: C, 59·2; H, 5·6. $C_{27}H_{30}O_9N_4$ requires C, 58·5; H, 5·4%).

5 : 7 : 4′-*triethoxy*-6-*methoxy isoflavone* (*XVII*)

The above ketone (XI) (1 g.) in freshly distilled ethyl formate (20 c.c.) was added to pulverised sodium (0·5 g.) well cooled in ice. The reaction was carried out as described in an analogous case. The isoflavone crystallised from methyl alcohol in the form of colourless needles melting at 140°. Yield

0·4 g. It gave no colour with ferric chloride and was insoluble in aqueous sodium hydroxide (Found: C, 68·6; H, 6·4. $C_{22}H_{24}O_6$ requires C, 68·8; H, 6·3%). Mixed m.p. with the triethyl ether obtained by ethylation of tectorigenin obtained from *Iris tectorum* (see below) was undepressed.

Triethyl ether of tectorigenin (XVII)

Tectorigenin (0·5 g.) was refluxed with ethyl iodide (0·5 c.c.) and anhydrous potassium carbonate (2 g.) in dry acetone solution (100 c.c.). After 40 hours the solution was filtered. The acetone was then distilled off and water added to the residue. The triethyl ether crystallised from methyl alcohol in the form of colourless needles melting at 140°. Yield 0·4 g. It gave no colour with ferric chloride and was insoluble in aqueous sodium hydroxide.

Oxime of p-*ethoxy phenyl pyruvic acid*

p-Ethoxy phenyl pyruvic acid was obtained by the method of Buck, Baltzly and Ide.[13]

A mixture of *p*-ethoxy phenyl pyruvic acid (10 g.) and hydroxyl amine (8 g.) in sodium hydroxide solution (100 c.c., 8%) was heated in a water-bath (60°) for 10 minutes and the solution left overnight. It was then cooled and acidified. The precipitated oxime was filtered and crystallised from alcohol when it came out as colourless tiny prisms, m.p. 168°. Yield 9 g. (Found: C, 58·9; H, 6·3. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·8%).

p-*Ethoxy phenyl acetic acid*

The dry oxime (5 g.) was treated with acetic anhydride (3 c.c.) and the mixture heated on the water-bath when a brisk evolution of carbon dioxide took place. After the reaction had subsided, water (50 c.c.) was added and the solution extracted with ether. The ether extract was washed with 5% sodium hydroxide and then with water. *p*-Ethoxy benzyl cyanide obtained on removal of the ether was directly hydrolysed to the acid, m.p. 87–9°. Yield 2 g.

Summary

Starting from antiarol a convenient synthesis of 2-methyl-5:6:7-trimethoxy (trihydroxy) and 5:6:7:4′-tetramethoxy isoflavones has been carried out. The intermediate ketones are satisfactorily obtained by the Friedel and Craft's reaction. Since the tetramethoxy isoflavone is identical with tectorigenin trimethyl ether the constitution of tectorigenin as a monomethyl ether of 5:6:7:4′-tetrahydroxy isoflavone is thus confirmed. The location of the methoxyl group is again fixed as 6- by complete ethylation

of tectorigenin and synthesis of this triethyl ether by a method analogous to the one described for the trimethyl ether.

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