SYNTHESIS OF SOME IMPORTANT PARTIAL METHYL ETHERS OF FLAVONOLS

By S. Rajagopalan, P. Ramachandra Rao, K. Visweswara Rao and T. R. Seshadri

(From the Department of Chemistry, Andhra University, Waltair)

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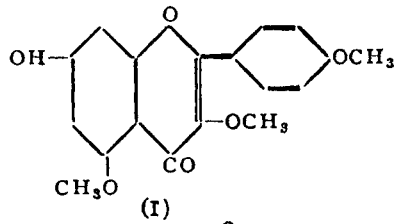
The most satisfactory method of locating the position of the sugar unit in the anthoxanthin glycosides is to carry out complete methylation and subsequently hydrolyse the product. The location of the hydroxyl group in the partial methyl ether thus produced will then settle the position of the sugar residue. The chief difficulties in the study of these partial methyl ethers are two: (1) they do not undergo fission with alkali satisfactorily; (2) except in a few favourable cases their synthesis is difficult. These difficulties can be overcome by employing the technique of ethylation and examining the mixed ethers of flavones thus produced. This procedure has been satisfactorily adopted in the case of gossypin,[1] hibiscitrin,[2] quercimeritrin and quercetagitrin[3] and populnin.[4] The synthesis of the partial methyl ethers themselves in some of the more difficult cases has now been accomplished with the help of partial benzylation. The method is capable of extension to the preparation of analogous compounds.

3 : 5 : 4′ : *O-Trimethyl-kæmpferol*

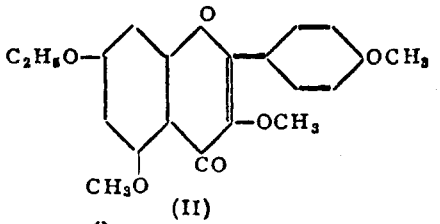
Populnin when methylated and hydrolysed yields a monohydroxy compound melting at 284–85°. Its constitution was determined by comparing it with all the known trimethyl ethers of kæmpferol having a free hydroxyl group in the 3, 5 and 4′ positions. Since it was different from these it was considered to be the 7-hydroxy isomer having the constitution (I). Conclusive evidence[4] was provided by the unambiguous synthesis of its ethyl derivative (II) and also of the fission ketone (III).

The above trimethyl ether of kæmpferol (7-hydroxy compound) was reported to have been obtained in the degradation of robinin and its properties as recorded by Zemplen and Bognar[5] agree with those of the partial methyl ether derived from populnin. The same compound was described by Nakamura and Hukuti[6] in connection with their study of equisetrin which is considered to be kæmpferol-7-diglucoside. The last mentioned authors described also its synthesis starting from the monomethyl ether of phloroglucinol which was first condensed with methoxy-acetonitrile (Hoesch

reaction). The resulting ketone (IV) was then subjected to the Allan-Robinson condensation with the anhydride and sodium salt of anisic acid.



(I)



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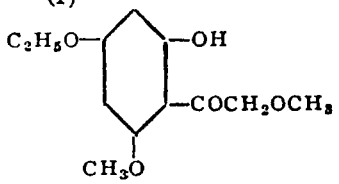

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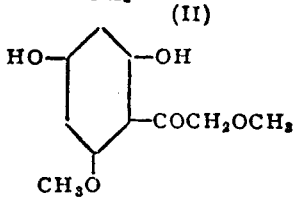
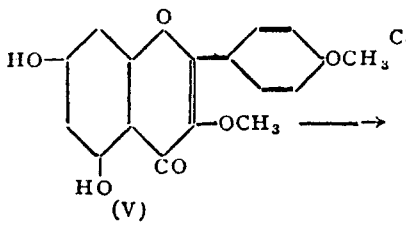


(IV)

In regard to this synthesis the preparation of the monomethyl ether of phloroglucinol in a pure state is time consuming. Further there is the possibility of demethylation occurring in the 5-position during the Allan-Robinson condensation.[7] Remethylation of this position without affecting others is not possible. In this connection it may be mentioned that Nakamura and Hukuti[6] recorded the melting point of the acetate of their synthetic product as 203° which is too high. A simpler synthesis of this reference compound which is free from defects should therefore be considered necessary. This has now been achieved by employing the technique of partial benzylation. The feasibility of this method in the flavone series was shown earlier in connection with the synthesis of wogonin.[8]

5 : 7-Dihydroxy-3 : 4′-dimethoxy flavone (V) has been recently subjected to partial benzylation using the requisite amount of benzyl chloride.[9] The reaction takes place in the 7-position leaving the resistant 5-hydroxyl free and the properties of the product agree with the requirements of the structure (VI). Subsequent methylation with excess of dimethyl sulphate and final debenzylation of (VII) using a mixture of concentrated hydrochloric acid and glacial acetic acid yield the 7-hydroxy-3 : 5 : 4′-trimethoxy flavone (I). This is found to be identical with the degradation product from populnin.



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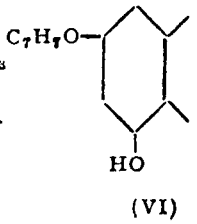
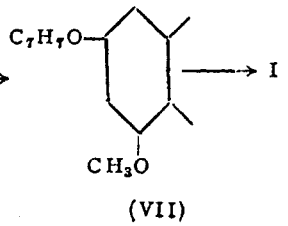


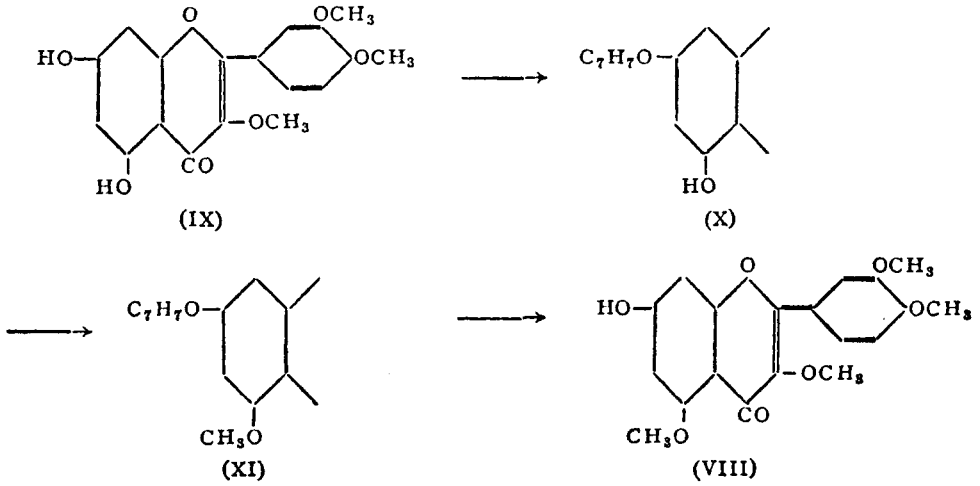
(VI)



(VII)

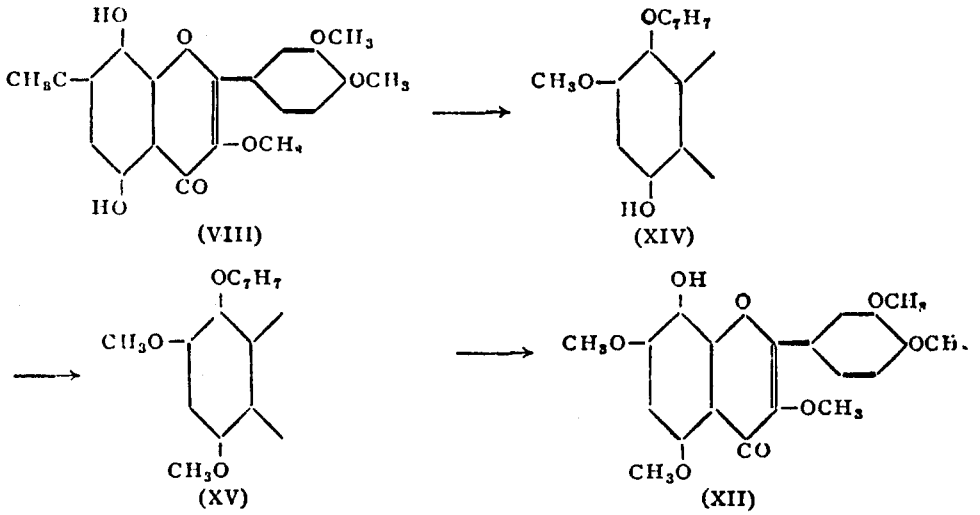
3 : 5 : 3′ : 4′-*O-Tetramethyl quercetin*

In an earlier paper[3] it was pointed out that the constitution of quercetin tetramethyl ether (VIII) obtained by the hydrolysis of methyl quercimeritrin was originally arrived at by Attree and Perkin[10] by eliminating other possibilities but no synthetic support was given. This was provided in that paper by ethylating the hydroxy compound (VIII) and showing that it is identical with 7-ethoxy-3 : 5 : 3′ : 4′-tetramethoxy flavone prepared synthetically. Following the same lines as given above for the partial methyl ether of kæmpferol and using the technique of partial benzylation the required quercetin tetramethyl ether has now been made, the starting point being 5 : 7-dihydroxy-3 : 3′ : 4′-trimethoxy flavone[11] (IX). The final product is found to be identical with the tetramethyl ether obtained from quercimeritrin by methylation and hydrolysis. For purposes of comparison the melting point of the hydroxy compound, its reactions with alkali and ferric chloride and the melting point of the acetate are used.



3 : 5 : 7 : 3′ : 4′-*O-Pentamethyl-gossypetin*

The third compound that has now been synthesised by this method is the pentamethyl ether of gossypetin (XII) obtained from gossypin. Its constitution was also first settled by the elimination of other possibilities[12] and later by an unambiguous synthesis of its ethyl ether.[1] The synthesis of the hydroxy compound itself starts from the quinol[13] (XIII) prepared by the persulphate oxidation of quercetin-tetramethyl ether and passes through the stages of partial benzylation of the 8-position, methylation and debenzylation as shown below. The synthetic product agrees in every respect with the compound obtained from gossypin.



Experimental

7-Benzyloxy-3 : 5 : 4′-trimethoxy-flavone (VII)

The preparation of 3 : 4′-dimethoxy-5-hydroxy-7-benzyloxyflavone (VI) has been recently described by Balakrishna and Seshadri.[9] It (0·5 g.) was dissolved in dry acetone (25 c.c.) and anhydrous potassium carbonate (5 g.) and dimethyl sulphate (0·5 c.c.) were added. The mixture was refluxed for 24 hours. The potassium salts were filtered off and washed with hot acetone. The filtrate was concentrated over a water-bath as far as possible and water was added to the residue when a brown solid separated out. It was filtered and crystallised first from alcohol and finally from ethyl acetate when it separated out slowly as colourless short rectangular plates and prisms melting at 118–20° with decomposition. (Found: C, 71·9; H, 5·5; $C_{25}H_{22}O_6$ requires C, 71·8; H, 5·4%.)

7-Hydroxy-3 : 5 : 4′-trimethoxy-flavone (I)

The above 7-benzyloxy compound (VII) (0·3 g.) was dissolved in glacial acetic acid (6 c.c.) and the solution was treated while hot with concentrated hydrochloric acid (4 c.c.). The mixture was kept at the temperature of the boiling water-bath for one hour. It was then diluted with water and set aside. A brown sticky solid separated out. It was filtered and crystallised twice from alcohol when it came out as colourless short needles melting at 283–85°. (Found: C, 66·1; H, 5·2; $C_{18}H_{16}O_6$ requires C, 65·9 and H, 4·9%.) The substance was soluble in alkali to form a light yellow solution and gave no colour with ferric cholride in alcoholic solution. It was only sparingly soluble in alcohol. The mixed melting point with the trimethyl ether

obtained from populnin after methylation and hydrolysis was undepressed. Its acetyl derivative was prepared by boiling with acetic anhydride and a few drops of pyridine. It crystallised from ethyl acetate or acetone in the form of colourless flat needles and narrow rectangular plates melting at 160–62°. Its mixed melting point with the acetate of the trimethyl ether from populnin was undepressed.

7-Benzyloxy-5-hydroxy-3 : 3′ : 4′-trimethoxy flavone (X)

5 : 7-Dihydroxy-3 : 3′ : 4′-trimethoxy flavone[11] (IX) (1·0 g.), dry acetone (30 c.c.), anhydrous potassium carbonate (5·0 g.) and benzyl chloride (0·25 c.c., 1 mol.) were employed and the benzylation carried out as mentioned before. The product was washed with petroleum ether and crystallised from ethyl acetate and petroleum ether mixture. It was obtained as fine yellow needles melting at 131–32°. Yield, 0·6 g. (Found: C, 69·2; H, 5·4; $C_{25}H_{22}O_7$ requires C, 69·1; H, 5·1%.) It was sparingly soluble in aqueous sodium hydroxide and gave a brown colour with alcoholic ferric chloride.

7-Benzyloxy-3 : 5 : 3′ : 4′-tetramethoxy flavone (XI)

The above 5-hydroxy compound (X) (0·5 g.) was methylated using dry acetone (25 c.c.), potassium carbonate (4·0 g.) and dimethyl sulphate (0·5 c.c.). The product crystallised from alcohol as colourless fine needles melting at 171–72°. Yield, 0·4 g. (Found: C, 69·5; H, 5·2; $C_{26}H_{24}O_7$ requires C, 69·6; H, 5·4%.) It was insoluble in aqueous sodium hydroxide and did not give any colour with alcoholic ferric chloride.

7-Hydroxy-3 : 5 : 3′ : 4′-tetramethoxy flavone: Quercetin tetramethyl ether (VIII)

The compound (XI) (0·3 g.) was debenzylated using concentrated hydrochloric acid (4 c.c.) and glacial acetic acid (6 c.c.). The quercetin tetramethyl ether (VIII) crystallised from alcohol acetic acid mixture as colourless rectangular plates melting at 284–85°. (Found: C, 63·7; H, 5·1; $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·0%.) It dissolved in aqueous sodium hydroxide to give a yellow solution and gave no colour with alcoholic ferric chloride. Its acetate crystallised from ethyl acetate as fine colourless needles melting at 174–75°. The above properties are identical with those of the compound obtained from quercimeritrin after methylation and hydrolysis. A mixed melting point of the two samples was undepressed.

8-O-Benzyl-3 : 7 : 3′ : 4′-O-tetramethyl gossypetin (XIV)

A solution of the quinol[13] (XIII) (1·0 g.) in acetone (50 c.c.), benzyl chloride (0·45 c.c.) and anhydrous potassium carbonate (5 g.) were employed.

The crude product was washed well with acidified water and finally with petroleum ether. It crystallised from acetone as lemon yellow needles melting at 159–60°. Yield, 1·1 g. (Found: C, 67·0; H, 5·4; $C_{26}H_{24}O_8$ requires C, 67·3; H, 5·2%.) It was sparingly soluble in alcohol but more easily in acetone and chloroform. It did not dissolve in aqueous sodium hydroxide but the colour of the solid changed to deep yellow on boiling. In alcoholic solution it gave an intense olive green colouration with ferric chloride.

8-*O-Benzyl-O-pentamethyl gossypetin* (*XV*)

The above monobenzyl ether (0·8 g.) was boiled with anhydrous acetone (50 c.c.), dimethyl sulphate (1 c.c.) and potassium carbonate (5 g.) for 12 hours. The solid product was washed well with aqueous alkali and subsequently with water. Recrystallisation of it from a mixture of alcohol and acetone yielded colourless long fibrous needles melting at 150–52°. (Found: C, 65·0; H, 5·8; $C_{27}H_{26}O_8$, H_2O requires C, 65·3; H, 5·6%.) Yield, 0·75 g. It was not soluble in alkali and it did not give any colour with alcoholic ferric chloride.

8-*Hydroxy*-3 : 5 : 7 : 3′ : 4′-*pentamethoxy flavone* (*XII*)

The debenzylation of the above compound (XV) (0·5 g.) was effected using glacial acetic acid (15 c.c.) and concentrated hydrochloric acid (3 c.c.). The yellow crystalline product obtained was washed thoroughly with water and then with light petroleum. It crystallised from alcohol as pale yellow rectangular plates melting at 196–98°. It gave a pale brown colour with ferric chloride and in all respects it was identical with the 8-hydroxy compound obtained from gossypin. The mixed melting point was undepressed. Yield, 0·2 g. Its acetate melted at 215–16° and was identical with the acetate of the 8-hydroxy compound obtained from gossypin.

Summary

The following three partial methyl ethers of flavonols which are derivatives of naturally occurring monoglucosides having only one free hydroxyl group have been conveniently synthesised by using the method of partial benzylation: (1) 3 : 5 : 4′-O-trimethyl-kæmpferol derived from populnin and related glycosides, (2) 3 : 5 : 3′ : 4′-O-tetramethyl quercetin derived from quercimeritrin and (3) 3 : 5 : 7 : 3′ : 4′-O-pentamethyl gossypetin derived from gossypin.

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