5:6:7:8-HYDROXYFLAVONOLS

Part II. A Total Synthesis

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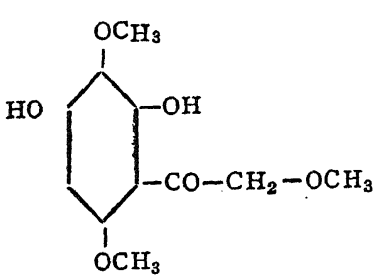
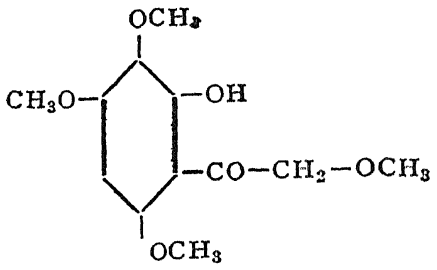
In a recent publication[1] which may now be considered as Part I of this series the preparation and properties of the four important members of this group of flavonols were described. They were made from 2-hydroxy-ω: 3: 4: 5: 6-pentamethoxyacetophenone which was itself obtained by the fission of calycopterin-dimethyl ether. A method of total synthesis has now been worked out and it is described in this communication.

ω : 3: 6-Trimethoxy-2: 4-dihydroxyacetophenone (I) was first prepared by Baker, Nodzu and Robinson[2] and its preparation was later simplified by Rao, Rao and Seshadri.[3] It has now been subjected to partial methylation yielding 2-hydroxy-ω: 3: 4: 6-tetramethoxyacetophenone (II). This compound is also known as gossypetol tetramethyl ether and was obtained earlier by the fission of gossypetin hexamethyl ether[4] and herbacetin pentamethyl ether[5] with alkali. The synthetic sample is identical with the natural one and the present work constitutes the first synthesis of this compound. Oxidation of this ketone with alkaline persulphate yields 2: 5-dihydroxy-ω: 3: 4: 6-tetramethoxyacetophenone (III). Partial methylation of this dihydroxy compound has been found to be very difficult. In only one of a number of experiments a very small yield of a crystalline sample agreeing in all its properties with 2-hydroxy-ω: 3: 4: 5: 6-pentamethoxyacetophenone could be obtained. Efforts are being made to get consistent yields. The dihydroxy ketone has been directly condensed with the sodium salt and anhydride of anisic acid and also of benzoic acid. The products (IV) yield on methylation the fully methylated ethers of calycopteretin and 6: 8-dihydroxygalangin respectively and on demethylation the free hydroxy flavonols.

The present synthesis yields as an important stage methyl ethers of the flavonols with a free hydroxyl in the 6-position. Possibilities exist of obtaining 5: 6-dihydroxy and 3: 5: 6-trihydroxy compounds by partial demethylation using hydrobromic acid and aluminium chloride.


(I)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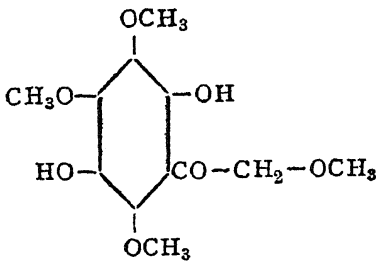
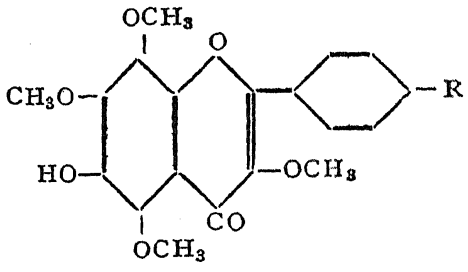

(III)


(IV)

R = H or OCH_3

EXPERIMENTAL

2 : 4-*Dihydroxy*-ω : 3 : 6-*trimethoxy-acetophenone* (I).—

In preparing this compound according to the method of Rao, Rao and Seshadri,[3] it is necessary to adhere very closely to the conditions prescribed in order to get a good yield of the main product and avoid as far as possible the by-product. The compound melted at 150-151° and had all the properties described in the literature.

2-*Hydroxy*-ω : 3 : 4 : 6-*tetra-methoxy-acetophenone* (*Gossypetol-tetramethyl ether*) (*II*).—

Method I.—The above dihydroxy ketone (2·4 g., 1·0 mol.) was treated with dimethyl sulphate (1·3 g., 1·1 mol.) and anhydrous potassium carbonate (2·0 g.) in anhydrous acetone (75 c.c.). The resulting mixture was refluxed for 12 hours and then filtered hot. The residue on the filter (A) was washed thrice with warm acetone. The acetone filtrate and washings were then evaporated to dryness. The solid residue was purified by dissolution in ether and extraction with aqueous alkali. The alkali extract on acidifying gave the 2-hydroxy-acetophenone free from the fully methylated derivative. It was crystallised from aqueous alcohol when it was obtained as short flat needles melting at 116-118°. Yield 1·6 g. (Found: C, 56·6; H, 6·6; $C_{12}H_{16}O_6$ requires C, 56·2; H, 6·3%).

From the potassium salt residue (A), a portion of the original dihydroxy ketone (0·3 g.) was recovered unchanged.

Method II.—Gossypetol tetramethyl ether was obtained by subjecting hexamethyl gossypetin to hydrolysis with 8% absolute alcoholic potash. For this purpose, gossypetin was methylated by means of excess of dimethyl sulphate and anhydrous potassium carbonate in anhydrous acetone medium. The hexamethyl gossypetin was crystallised from ethyl acetate when it was obtained as almost colourless needles melting at 170-172°.

Hexamethyl gossypetin (2·0 g.) was refluxed with absolute alcoholic potash (8%, 45 c.c.) for about 6 hours. The alcohol was then removed under reduced pressure and the residue dissolved in water (75 c.c.) and acidified with hydrochloric acid. The turbid solution was repeatedly extracted with ether and the combined ethereal extracts shaken with aqueous sodium bicarbonate solution to remove the veratric acid which was a product of hydrolysis. The ether layer was then washed with water, dried over anhydrous sodium sulphate and the solvent distilled off. The residue turned into a crystalline solid on cooling. It crystallised from aqueous alcohol in the form of short flat needles melting at 116-118°. Yield, 0·8 g. It did not depress the melting point of the ketone obtained by method I.

2-Hydroxy ω-: 3: 4: 6-tetramethoxy-acetophenone was soluble in aqueous alkali rather sparingly yielding an almost colourless solution. With ferric chloride, a reddish brown colouration was developed in alcoholic solution.

2 : 5-*Dihydroxy*-ω : 3 : 4 : 6-*tetramethoxy-acetophenone* (*III*).—

To a mechanically stirred solution of gossypetol tetramethyl ether (2·6 g.) in aqueous sodium hydroxide (1·5 g. in 50 c.c.) kept between 15-20°, was added potassium persulphate solution (3·0 g. in 50 c.c. of water) little by little during the course of three hours. The solution which was almost colourless at first, gradually changed through pale reddish brown to deep reddish brown during the course of the addition. After leaving the solution overnight it was made neutral to litmus with dilute hydrochloric acid and extracted twice with ether to remove the unoxidised gossypetol tetramethyl ether (0·2–0·3 g.). The aqueous solution was then rendered strongly acidic by adding concentrated hydrochloric acid (10 c.c.). Benzene (50 c.c.) was then added to this liquid and the mixture refluxed on the water-bath for about half an hour. While still warm, the benzene layer was separated and the aqueous layer extracted twice with benzene. The combined benzene extracts were cooled and dried over sodium sulphate. After distilling off the benzene, the semi-solid residue was crystallised from benzene-petroleum ether mixture (1 : 1) when the 2 : 5-dihydroxy-ketone was obtained as bright yellow rectangular plates melting at 102–103°. A

second crystallisation was also done from the same solvent; but there was no improvement in the melting point. Yield, 0·4 g. It dissolved readily in aqueous alkali yielding a reddish yellow solution. A transient green colour was obtained with ferric chloride in alcoholic solution, the colour changing rapidly to brown; after half an hour it was deep reddish brown. (Found: C, 53·0; H, 6·3; $C_{12}H_{16}O_7$ requires C, 52.9 and H, 5·9%).

6-Hydroxy-3:5:7:8:4'-Pentamethoxy-flavone (IV).—

The above dihydroxy ketone (0·8 g.) was subjected to Allan and Robinson condensation with anisic anhydride (2·0 g.) and sodium anisate (0·8 g.) by heating at 170–180° for about four hours. After hydrolysis with 10% alcoholic alkali, the alcohol was removed under reduced pressure and the solid product dissolved in water (125 c.c.). After saturating the alkaline liquid with carbon dioxide, it was extracted repeatedly with ether. When the ether extract was distilled, a bright yellow crystalline residue was obtained. It was crystallised twice from alcohol. The 6-hydroxy-flavone came out in the form of stout rectangular prisms melting at 160–161° with slight sintering at 159°. Yield, 0·4 g. It was easily soluble in aqueous alkali yielding a bright yellow solution. It gave no marked colour with ferric chloride in alcoholic solution. (Found: C, 61·8; H, 5·4; $C_{20}H_{20}O_8$ requires C, 61·8 and H, 5·2%).

Calycopterin-dimethyl ether.—

The above 6-hydroxy flavone (0·3 g.) was methylated with excess dimethyl sulphate (0·3 c.c.) and anhydrous potassium carbonate (0·3 g.) in anhydrous acetone medium. After refluxing for 20 hours, the acetone solution was filtered and the residue on the filter washed thrice with warm acetone. When the filtrate was evaporated, a colourless crystalline solid was left behind which was crystallised twice from aqueous alcohol. The methyl ether was thus obtained in the form of colourless long needle-shaped crystals melting at 131–132°. It did not depress the melting point of an authentic sample of calycopterin dimethyl ether. Yield, 0·2 g.

Calycopteretin.—

The above sample of calycopterin dimethyl ether (0·15 g.) was demethylated by refluxing for an hour with hydriodic acid (d. 1·7, 2·5 c.c.) and acetic anhydride (1·5 c.c.). After demethylation, the liquid was cooled and diluted with sulphur dioxide water. The precipitated flavone was filtered and washed with water. The solid was yellow in the beginning but gradually turned greenish yellow. It was dried in a desiccator and crystallised twice from dry ethyl acetate. Calycopteretin was thereby

obtained in the form of deep yellow tiny rectangular plates melting with decomposition at 318–20°. The mixed melting point with an authentic sample of calycopteretin was undepressed. The colour reactions in alkaline buffer solutions were also identical. (Found: C, 56·6; H, 3·5; $C_{15}H_{10}O_8$ requires C, 56·6 and H, 3·2%).

3:5:6:7:8-*Pentamethoxy-flavone.*—

The dihydroxy ketone III (1·0 g.) was condensed with benzoic anhydride (3·0 g.) and sodium benzoate (1·0 g.) using the conditions already described. After hydrolysis, the alkaline liquid was saturated with carbon-dioxide and the flavone recovered by ether extraction. It was pale yellow and gave brownish green colour with ferric chloride in alcoholic solution, indicating the presence of a free 5-hydroxyl. The solid was therefore dried in a vacuum desiccator and methylated completely with dimethyl sulphate (1·0 c.c.) and anhydrous potassium carbonate (1·0 g.) in anhydrous acetone medium. After refluxing for 20 hours, the solution was filtered and the potassium salts washed with warm acetone (20 c.c.). On distilling off the solvent from the filtrate a colourless crystalline solid was obtained. It gave no colour with ferric chloride in alcoholic solution. When further crystallised from aqueous alcohol it was obtained as colourless long needles melting at 81–82°. The mixed melting point with an authentic sample of the pentamethoxy-flavone was undepressed. Demethylation of this ether with hydriodic acid yielded 6:8-dihydroxygalangin as yellow rectangular plates melting at 257–258° and identical with an authentic sample described already.[1]

Summary

A method of complete synthesis of 5:6:7:8-hydroxy flavonols is described. It starts from ω: 3: 6-trimethoxy-2: 4-dihydroxy-acetophenone which is subjected to partial methylation (of the 4-hydroxyl group) and subsequently to persulphate oxidation. The product, 2: 5-dihydroxy-ω: 3: 4: 6-tetramethoxy-acetophenone is condensed with the anhydride and sodium salt of anisic acid and also of benzoic acid. The resulting 6-hydroxy-flavones yield on further methylation the fully methylated ethers of calycopteretin and 6:8-dihydroxy-galangin and on demethylation, the free hydroxy-flavonols.

References

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4. Perkin .. *J.C.S.*, 1913, **103**, 650.
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