SYNTHESIS OF HIBISCETIN

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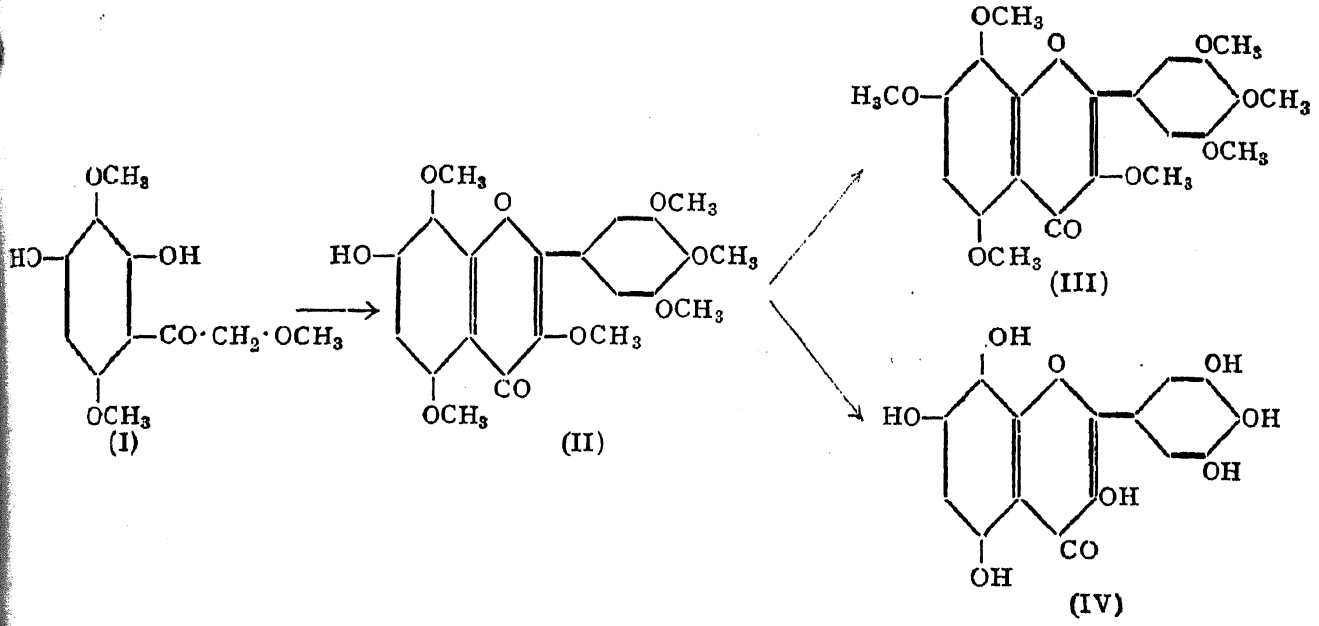
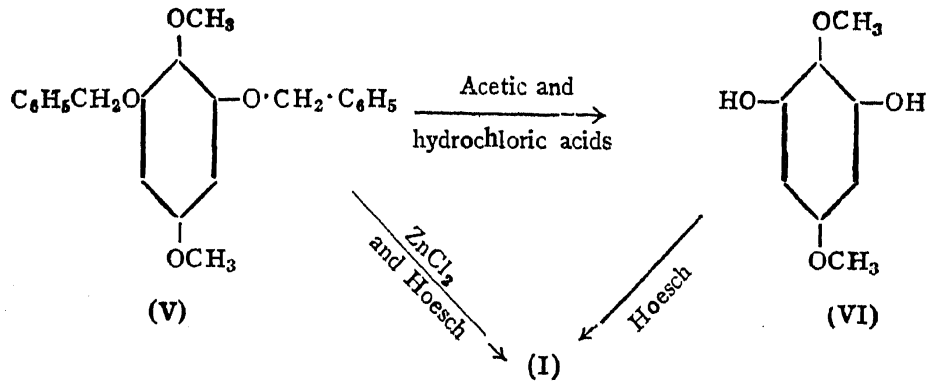
IT has recently been shown that the glucoside, Hibiscitrin is the main pigment component of the flower petals of *Hibiscus sabdariffa*, gossypitrin and sabdaritrin being present in minor quantities.[1] The aglucone, hibiscetin has the formula $C_{15}H_{10}O_9$ and has seven hydroxyl groups thereby forming heptamethyl and hepta-acetyl derivatives. It is therefore one of the most highly hydroxylated compounds among flavones and flavonols. It gets readily oxidised in alkaline solutions. When its heptamethyl ether is decomposed with alcoholic potash, trimethyl gallic acid is formed as one of the products. In its reactions with alkaline buffer solutions and with *p*-benzoquinone it closely resembles herbacetin and gossypetin. Based on these results Rao and Seshadri proposed for it the constitution of 3:5:7:8:3′:4′:5′-heptahydroxy flavone.[2] It is thus the highest member of the herbacetin series of flavonols and carries three hydroxyl groups in the side phenyl nucleus.

The above constitution of hibiscetin has now been confirmed by synthesis. The method adopted is very similar to that employed by Baker, Nodzu and Robinson for the synthesis of gossypetin.[3] 2:4-Dihydroxy-ω:3:6-trimethoxy-acetophenone (I) is condensed with the sodium salt and anhydride of trimethyl gallic acid. The product is 7-hydroxy-3:5:8:3′:4′:5′-hexamethoxy flavone (II) which when methylated, readily yields the heptamethyl ether (III) melting at 194–96°. Its identity with hibiscetin heptamethyl ether has been established by a mixed melting-point determination. A preliminary report on this identity has been made by Rao[4] in *Current Science*. Demethylation of (II) using hydriodic acid gives rise to 3:5:7:8:3′:4′:5′-heptahydroxyflavone (IV) melting with decomposition at about 350°. A mixture of this with hibiscetin obtained from the flowers of *Hibiscus sabdariffa* behaves similarly. Further comparison of the composition melting points and the colour reactions (using dilute alkali, ferric chloride and alkaline buffer solutions) of the synthetic and natural samples has confirmed complete identity.[2]



For the preparation of the ketone (I) the original method of Baker *et al.*[3] involved the following stages. The tribenzyl ether of pyrogallol was oxidised by means of nitric acid to 2:6-dibenzyloxy-*p*-benzoquinone. This was reduced to the corresponding quinol and methylated leading to the formation of 2:6-dibenzyloxy-1:4-dimethoxybenzene (V). Since benzyl ethers are much more readily hydrolysed than methyl ethers, debenzylation of (V) could be effected by the action of a mixture of hydrochloric and acetic acids at 65° and 2:5-dimethoxy resorcinol (VI) was obtained. This was subsequently converted to the ketone (I) by the application of Hoesch reaction using methoxy acetonitrile. The above method of debenzylation is not convenient and considerable drop in yield is sustained during the operation. The preparation of the ketone has now been rendered simpler and the yield considerably improved by a modification in the above procedure. When compound (V) is treated with methoxy acetonitrile and dry hydrogen chloride



in ethereal solution in the presence of anhydrous zinc chloride the ketimine hydrochloride corresponding to (I) is formed. Obviously debenzylation

and Hoesch condensation have taken place together. The presence of zinc chloride is quite necessary as otherwise no reaction takes place. Since (VI) undergoes Hoesch condensation in the absence of zinc chloride it could be inferred that this salt (in conjunction with hydrogen chloride) is responsible for the debenzylation which seems to be a necessary preliminary to the subsequent Hoesch condensation.

Experimental

2: 4-*Dihydroxy-ω*: 3: 6-*trimethoxy acetophenone*.—2: 6-dibenzyloxy-1: 4 dimethoxy benzene (7 g.) prepared from pyrogallol according to the procedure adopted by Baker, Nodzu and Robinson[3] was dissolved in dry ether (75 c.c.) and methoxy-acetonitrile (3·5 g.) added. After the addition of anhydrous zinc chloride (3 g.), the mixture was saturated with dry hydrogen chloride at 0°, and the current of gas passed further for nearly four hours. The flask was then corked tightly, sealed with wax and left overnight in a refrigerator. The ketimine hydrochloride was formed as a dark brown semi-solid with a pale yellow incrustation. Further quantity was precipitated by the addition of dry ether. It was separated, and washed with more of ether. The original ether solution and the washings contained mainly benzyl chloride. The ketimine hydrochloride was dissolved in water (50 c.c.), and the solution (A) extracted with ether to remove impurities. The ether extract, which was slightly turbid, yielded on evaporation a sticky substance. When purified by crystallisation from alcohol using a little animal charcoal it was obtained as a colourless crystalline solid melting at 110°–12°. It gave a light violet colour with ferric chloride. The yield of this by-product was very variable and it went up to a maximum of 0·5 g. in one experiment. Its nature is still under investigation.

When the ketimine hydrochloride solution (A) was heated on the water-bath for an hour and cooled, the crude ketone crystallised out. Further quantities could be obtained by the concentration of the mother-liquor and extraction with ether. The crude compound was easily soluble in sodium carbonate solution, while the accompanying impurities were not. This property was made use of in the preliminary purification of the compound. It was finally crystallised from hot water, when it came out as long colourless needles melting at 150–51°. With ferric chloride an alcoholic solution of the substance gave a bluish violet colouration. The yield of the pure product was 3 g.

7-*Hydroxy*-3: 5: 8: 3′: 4′: 5′-*hexamethoxy flavone* (*hexamethyl hibiscetin*).—2: 4-Dihydroxy-*ω*: 3: 6-trimethoxy acetophenone (2 g.), sodium trimethyl gallate (8 g.) and trimethyl gallic anhydride (20 g.) were intimately

mixed together and heated under reduced pressure for four hours in an oil-bath at 175–80°. During heating there was some resinification of the material. The reaction product was dissolved in boiling alcohol (150 c.c.) and treated with 40% potassium hydroxide (20 c.c.) in small quantities during the course of 20 minutes. The mixture was then boiled under reflux for half an hour. The solvent was subsequently removed under reduced pressure, the residue dissolved in water (100 c.c.) and the solution saturated with carbon dioxide. As no flavonol separated out at this stage, the clear alkaline solution was treated with hydrochloric acid till the reaction was just acid and the precipitated trimethyl gallic acid rapidly filtered under suction. When the filtrate was extracted with ether and the solution evaporated, a pale yellow substance was obtained. It was washed with cold dilute sodium carbonate in order to remove the last traces of trimethyl gallic acid and was finally crystallised from dilute acetic acid. It was thus obtained as light yellow needles and rectangular plates melting at 238–40°. The yield was 0·5 g. [Found in air-dried material: C, 59·7; H, 5·7; $C_{15}H_3O_2$ (OH) $(OCH_3)_6$ requires: C, 60·3; and H, 5·3%.] The substance dissolved in alkali to form a yellow solution and developed no characteristic colour with ferric chloride.

3 : 5 : 7 : 8 : 3′ : 4′ : 5′-*Heptamethoxy flavone* (*heptamethyl hibiscetin*).—The hexamethyl hibiscetin (0·2 g.) was dissolved in 20% sodium hydroxide (5 c.c.) and treated with dimethyl sulphate (0·5 c.c.) in drops with vigorous shaking. During the operation, the methylated product began to separate out, but the reaction was brought to completion by heating the mixture on a water-bath for half an hour. On cooling, the methyl ether precipitated out completely. It crystallised from dilute acetic acid as shining colourless needles and narrow rectangular plates melting at 194–96°. Mixed melting point with heptamethyl hibiscetin, prepared by the methylation of hibiscetin, was undepressed.

3 : 5 : 7 : 8 : 3′ : 4′ : 5′-*Heptahydroxy flavone* (*hibiscetin*).—The hexamethyl hibiscetin obtained above (0·2 g.) was dissolved in acetic anhydride (0·5 c.c.) and treated with hydriodic acid (5 c.c.) of 1·7 density. The mixture was boiled under reflux for 3 hours. After dilution with an equal amount of water, sulphur dioxide was passed through the solution in order to remove iodine. A yellow solid was then found to have separated out. It was insoluble in all the ordinary organic solvents except dilute pyridine from which it crystallised as deep yellow shining rectangular plates and prisms melting at about 350° with decomposition. It dissolved, like the natural hibiscetin, in dilute alkali producing a red solution which rapidly changed to brown. With neutral lead acetate it gave a deep red

precipitate in alcoholic solution and with ferric chloride an olive brown colour. With alkaline buffer solutions its colour changes were exactly similar to those produced with the natural pigment; the initial deep yellow solution rapidly changed to green and then to blue; this colour quickly faded to brown and was pale yellow after 24 hours. [Found: C, 50·6; H, 3·8; $C_{15}H_{10}O_9$, H_2O requires C, 51·1; H, 3·4.]

Summary

A convenient method of preparing 2:4-dihydroxy-ω:3:6-trimethoxy-acetophenone (I) directly from 2:6-dibenzyloxy-1:4-dimethoxybenzene is described. By the condensation of (I) with the sodium salt and anhydride of trimethylgallic acid, 7-hydroxy-3:5:8:3′:4′:5′-hexamethoxyflavone (II) is obtained. Methylation of (II) yields a heptamethyl ether (III) identical with heptamethyl hibiscetin. Demethylation of (II) gives rise to a heptahydroxy flavone (IV) which is found to be identical with hibiscetin in all its properties and reactions. The constitution of hibiscetin is therefore confirmed by synthesis as 3:5:7:8:3′:4′:5′-heptahydroxy flavone.

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