NUCLEAR OXIDATION IN THE FLAVONE SERIES

Part IV. New Synthesis of Herbacetin and Hibiscetin

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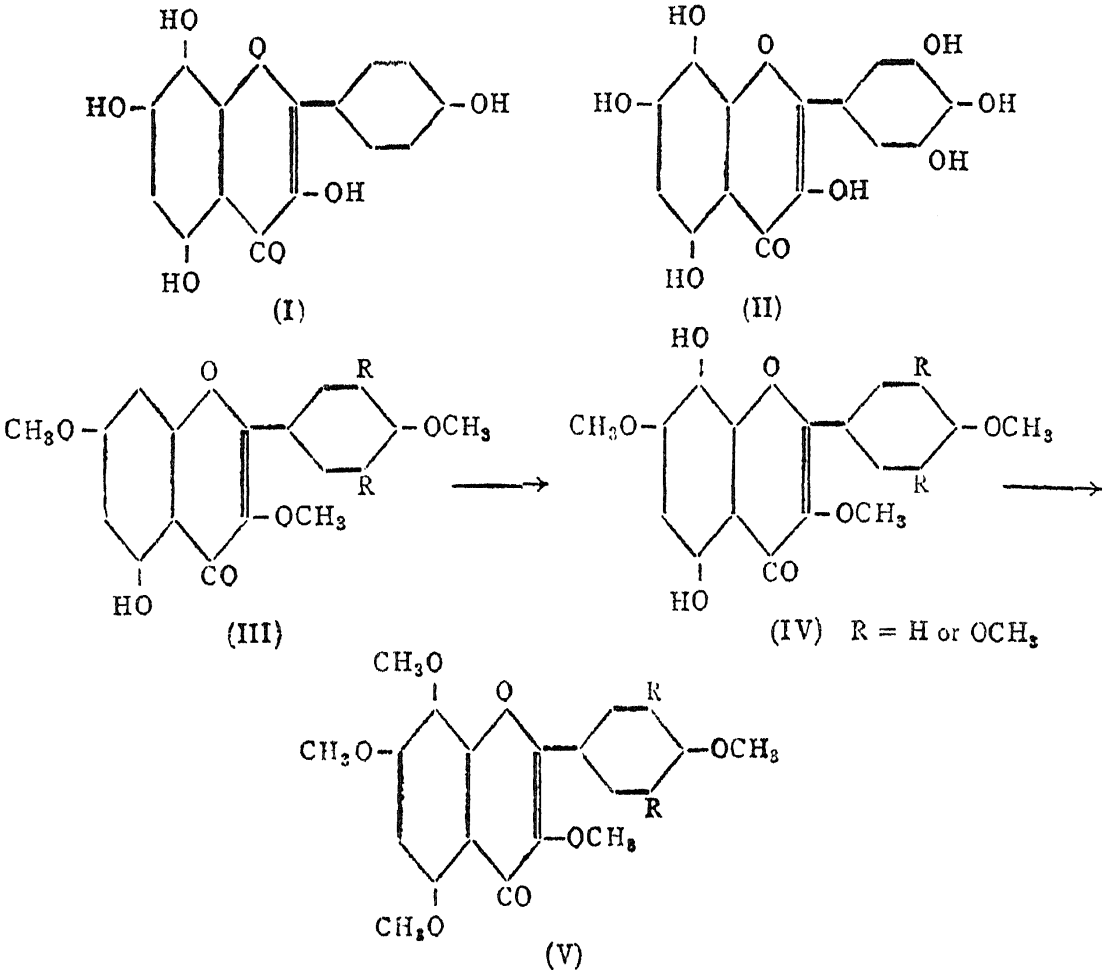
In Part I[1] was described the synthesis of gossypetin and 8-hydroxy-galangin by the nuclear oxidation of quercetin and galangin derivatives. Herbacetin (I) and Hibiscetin (II) are the other two members of this flavonol series with the 5:7:8-arrangement of hydroxyl groups. The former was first isolated by Neelakantam and Seshadri[2] from the flowers of Gossypium herbaceum and was later found to occur in the flowers of *Thespasia populnea*[3] also. Its partial methyl ether, tambulin is present in the fruits of *Zanthoxylum acanthopodium*.[4] It was first synthesised by Goldsworthy and Robinson[5] using 2:4-hydroxy-ω:3:6-trimethoxyacetophenone as the important intermediate. Hibiscetin occurs as the main component of the flowers of *Hibiscus sabdariffa*[6]; it has been synthesised by Rao, Rao and Seshadri[6] employing the above mentioned ketone.

These two flavonols have now been prepared synthetically in good yields by means of the new method of nuclear oxidation in the 8-position. Kæmpferol obtained from the flowers of *Thespasia populnea* and myricetin from the flowers of *Hibiscus cannabinus* have been employed for this purpose. As in the previous cases these were first methylated partially leaving the hydroxyl in the 5-position alone free and subsequently subjected to oxidation with persulphate. A synthetic sample of 3:3′:4′:5′-O-tetramethyl-myricetin[7] having free hydroxyls in the 5 and 7 positions has also been used. The 5:7:8-trihydroxy compound obtained in this case is only pale yellow in colour whereas the lower analogues are deeper. Such weakening of colour with increase in the number of methoxyls in the side phenyl nucleus has been noted in other cases also.[8] The reactions of the 5:8-dihydroxy and 5:7:8-trihydroxy-compounds are quite similar to those of the analogous compounds described in Part I.

3:7:4′-O-trimethyl herbacetin (IV, R= H) has also been prepared by the oxidation of herbacetin pentamethyl ether (V, R =H) with nitric acid and the reduction of the quinone thus produced.



The above synthesis establishes the biogenetic relationship between herbacetin and kæmpferol and between hibiscetin and myricetin. The first two have been found to occur together in the Indian cotton flowers and in the flowers of *Thespasia populnea*. Though myricetin has not been definitely detected in the flowers of *Hibiscus sabdriffa* which contain hibiscetin, it occurs as the main component of the flowers of the closely allied species, *H. cannabinus*.

Experimental

For the preparation of the required partial methyl ether (III), kæmpferol or myricetin was boiled in dry acetone solution with the correct quantity of dimethyl sulphate (3 or 5 mols.; a very small excess is better) and excess of anhydrous potassium carbonate for six hours. Distillation of the solvent and addition of water yielded the crude product. It was purified by conversion into the potassium salt and regeneration. Kæmpferol-trimethyl-ether melted at 152–53° and myricetin penta-methyl ether at 138–39° as reported in the literature.[9]

3:7:4′-*Trimethoxy*-5:8-*dihydroxy-flavone* (IV, R= H)

(*a*) *By oxidation with persulphate.*—A solution of 3:7:4′-trimethoxy-5-hydroxy-flavone (III, R = H) (0·6 g.) in a mixture of pyridine (15 c.c.)

and aqueous potassium hydroxide (0·6 g. in 40 c.c.) was vigorously stirred and treated dropwise with an aqueous solution of potassium persulphate (0·8 g. in 50 c.c.) during the course of 2 hours. The deep green solution was kept for 24 hours and then rendered slightly acidic to Congo Red. The brown solid that separated out was filtered off and the filtrate extracted twice with ether (20 c.c. each time). The clear brown solution was treated with sodium sulphite (2 g.) and concentrated hydrochloric acid (20 c.c.) and kept in a boiling water-bath for 30 minutes during which time a yellowish brown crystalline solid separated out. It was filtered off after cooling the solution and washed free from acid. On extracting the filtrate with ether a little more was obtained. Yield 0·3 g. Crystallisation from alcohol yielded shining yellow rectangular plates and prisms melting at 196–98° (Found: C, 62·8; H, 4·4; $C_{18}H_{16}O_7$ requires C, 62·8; H, 4·7%). It was sparingly soluble in alcohol and ethyl acetate. In 5% aqueous sodium hydroxide it readily dissolved to a deep red solution which turned to bluish violet in a few minutes. It gave with ferric chloride in alcoholic solution a green colour which changed to brown. With *p*-benzoquinone in alcoholic solution a deep red colour was obtained with the gradual deposition of a red crystalline solid.

The dihydroxy compound (IV) (0·1 g.) was dissolved in dry acetone (25 c.c.) and treated with dimethyl sulphate (0·5 c.c.) and anhydrous potassium carbonate (5 g.). After refluxing for 6 hours the solvent was distilled off and the residue treated with water. The methyl ether was filtered and crystallised from alcohol when it came out in the form of colourless narrow rectangular plates melting at 154–56° alone or in admixture with an authentic sample of the pentamethyl ether of herbacetin.

(*b*) *By demethylation with nitric acid.*—Nitric acid (4 c.c.; d, 1·25) was added to herbacetin-pentamethyl-ether (V, R= H, 0·2 g.) with vigorous stirring while keeping the temperature below 15°. The substance dissolved to a yellow solution which soon changed to orange and finally deep red. A deep red product separated which soon solidified in a few minutes. It was filtered off and washed with nitric acid (d, 1·25) followed by water. Crystallisation from alcohol yielded deep red spear shaped crystals melting at 220–22°. It was sparingly soluble in alcohol. It readily dissolved in aqueous sodium hydroxide to an intense bluish violet solution. When a solution of the substance in acetic acid was treated with aqueous sodium sulphite a bright yellow solid separated which on crystallisation from alcohol came out in the form of yellow rectangular plates melting at 196–98° identical with the dihydroxy compound (IV, R= H) obtained by the oxidation of 5-hydroxy-3 : 7 : 4′-trimethoxy-flavone (III).

5: 8-*Dihydroxy*-3: 7: 3′: 4′: 5′-*pentamethoxy-flavone* (IV, R= OCH_3)

To a stirred solution of 3:7:3′:4′:5′-O-pentamethyl myricetin (III, R = OCH_3) (1 g.) in a mixture of pyridine (20 c.c.) and aqueous potassium hydroxide (0.75 g. in 25 c.c.) was added dropwise a solution of potassium persulphate (1 g. in 50 c.c.) during the course of 2 hours. The colour of the solution first changed to intense olive green and then gradually to deep brown. After keeping it for 24 hours it was just acidified, the pale brown solid that separated out was filtered and the filtrate extracted with ether twice. The clear brown aqueous layer was then treated with sodium sulphite (2 g.) and concentrated hydrochloric acid (25 c.c.) and kept in the boiling water bath for 30 minutes. The yellowish brown solid that separated out was filtered off and washed well; the filtrate on ether extraction yielded some more of the product. Yield 0.5 g. It was crystallised twice from alcohol from which it came out in the form of lustrous golden yellow long rectangular prisms and rods melting at 200–202°. (Found: C, 59.7; H, 4.6; $C_{20}H_{20}O_9$ requires C, 59.4; H, 5.0%). It was readily soluble in aqueous sodium hydroxide to a deep red coloured solution which changed to bluish violet in a few minutes. In alcoholic solution it gave with ferric chloride a transient green colour which changed to brown. With *p*-benzoquinone a reddish brown colour was obtained together with the slow deposition of a red solid.

The dihydroxy compound (0.2 g.) was methylated by boiling for 6 hours with dry acetone (25 c.c.), dimethyl sulphate (0.5 c.c.) and anhydrous potassium carbonate (5 g.). When crystallised from alcohol the methyl ether separated in the form of colourless rectangular plates melting at 192–93°. Mixed melting point with an authentic sample of hibiscetin-hepta-methyl-ether (V, R= OCH_3) was not depressed.

5: 7: 8-*Trihydroxy*-3: 3′: 4′: 5′-*tetramethoxy-flavone*

A stirred solution of 3: 3′: 4′: 5′-tetramethyl ether of myricetin[7] (1 g.) in aqueous potassium hydroxide (1 g. in 30 c.c.) was treated with potassium persulphate solution (1 g. in 50 c.c.) drop by drop for 2 hours. The deep brown solution was kept for 24 hours and neutralised. The brown solid precipitate was filtered off and the filtrate extracted with ether twice. The aqueous solution was treated with sodium sulphite (2 g.) and concentrated hydrochloric acid (25 c.c.) and kept in a boiling water bath for 30 minutes. The glistening brown crystalline solid that separated out was filtered and washed. The filtrate yielded some of the substance on extraction with ether. Yield 0.55 g. Crystallisation from alcohol and subsequently from ethyl acetate yielded pale yellow short rectangular plates and prisms melting at 257–58° (Found: C, 58.3; H, 4.3; $C_{19}H_{18}O_9$ requires C, 58.5; H,

4.6%). It was very sparingly soluble in ethyl acetate. With ferric chloride in alcholic solution it gave a deep greenish brown colour. In 5% sodium hydroxide it dissolved quickly to form a deep brown red solution wich soon faded to a pale blue colour. In 5% sodium carbonate it dissolved to a brown solution wich changed to pale greenish yellow.

Methylation of the trihydroxy compound (0.1 g.) in anhydrous acetone medium (20 c.c.) with dimethyl sulphate (0.5 c.c.) and potassium carbonate (5 g.) yielded the heptametyhl ether which crystallised from alcohol in the form of colourless rectangular plates melting at 192-93° identical with the heptamethyl ether of hibiscetin (V, R= OCH_3).

Summary

The synthesis of herbacetin and hibiscetin from kæmpferol and myricetin is described. As before, the partial methyl ethers of the latter have been subjected to nuclear oxidation with alkaline persulphate. The oxidation proceeds smoothly and gives rise to good yields of the products.

References

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