NUCLEAR OXIDATION IN THE FLAVONE SERIES

Part VI. A New Synthesis of Calycopteretin and 6 : 8-Dihydroxy-quercetin

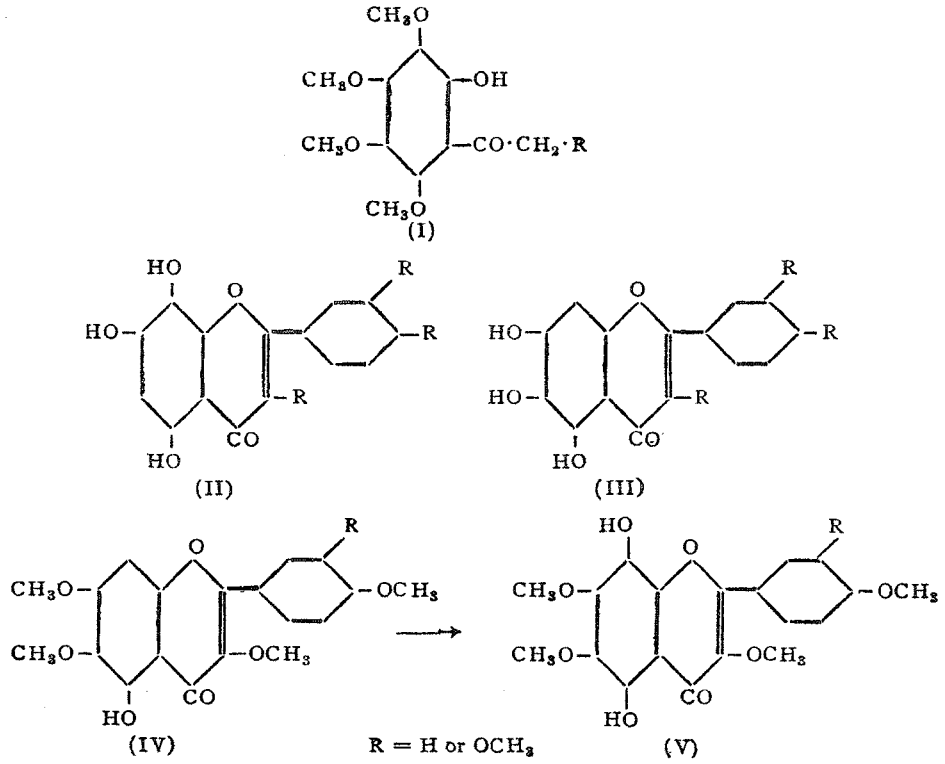
BY S. RAJAGOPALAN, K. VISWESWARA RAO AND T. R. SESHADRI, F.A.SC.

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

Received May 12, 1947

5 : 6 : 7 : 8-Hydroxy-flavones and flavonols form an important group of highly hydroxylated compounds and several of them and related substances occur in nature. In the earlier synthesis of these compounds, suitable derivatives (methyl ethers) of pentahydroxy-acetophenone (I) were employed and the required flavone or flavonol molecule built up. Thus were synthesised nobiletin by Horii[1] and all the main flavonols of the calycopteretin series by workers in this laboratory.[2] An alternative method which is of interest from the point of view of biogenesis will be by nuclear oxidation of the appropriate lower member. In this connection these flavonols can be viewed in either of two ways, (1) as oxidation products of 5 : 7 : 8-hydroxy-flavones or flavonols (II) or (2) as oxidation products of 5 : 6 : 7-hydroxy-flavones and flavonols (III). Attempts made to oxidise 3 : 7 : 8 : 3′ : 4′-O-pentamethyl-gossypetin with a hydroxyl free in the 5-position under the ordinary conditions, were not successful; ortho oxidation does not seem to take place so readily. On the other hand, the isomeric quercetagetin-pentamethyl ether (IV, R = OCH_3) undergoes oxidation very readily and gives rise to a good yield of the corresponding quinol (V, R= OCH_3). Methylation of this yields the heptamethyl ether of 6 : 8-dihydroxy-quercetin and demethylation the free flavonol itself. For this purpose quercetagetin obtained from the flowers of *Tagetes erecta*[3] was employed and subjected to partial methylation using the correct quantities of dimethyl sulphate and potassium carbonate. In a similar manner the tetramethyl ether of nor-tangeretin (IV, R= H) was made from a synthetic sample[4] and this was subjected to oxidation. The quinol (V, R= H) on methylation yielded calycopterin dimethyl ether and on demethylation calycopteretin itself.

From the abovementioned results it would appear that compounds with the 5 : 6 : 7-arrangement of hydroxyl groups are the precursors of the compounds of the nobiletin and calycopterin series. In this connection may be mentioned the observation that nobiletin (5 : 6 : 7 : 8 type) is found in the peels of the Chinese Mandarin oranges,[5] *Citrus nobilis* and tangeretin



(5:6:7: type) in the closely related American Tangerines,[6] *Citrus nobilis deliciosa.*

Experimental

O-Pentamethyl-quercetagetin (IV, R= OCH_3):

A solution of quercetagetin (1·5 g.) in anhydrous acetone (75 c.c.) was treated with dimethyl sulphate (2·5 c.c.) and anhydrous potassium carbonate (10 g.). After refluxing for 6 hours, the solvent was distilled off and the residue treated with water when a yellowish brown solid was left behind. It was filtered, washed with water and crystallised twice from alcohol when it separated out in the form of pale yellow rectangular prisms melting at 158–60°. It was sparingly soluble in aqueous sodium hydroxide and gave a greenish brown colour with ferric chloride in alcoholic solution. The original alkaline filtrate on acidification did not give any appreciable amount of solid.

5:8-Dihydroxy-3:6:7:3':4'-pentamethoxy-flavone (V, R= OCH_3):

O-Pentamethyl-quercetagetin (IV) (1 g.) was dissolved in a mixture of pyridine (20 c.c.) and aqueous potassium hydroxide (0·8 g. in 25 c.c.) and

the clear yellowish brown solution was stirred and treated with aqueous potassium persulphate (1 g. in 50 c.c.) gradually during the course of two hours. The deep olive brown solution was allowed to stand for 24 hours and then rendered slightly acidic when a light brown precipitate was formed. It was filtered off and washed with water; yield 0·3 g. It was found to be almost pure pentamethyl quercetagetin. The filtrate was extracted twice with ether and the clear brown aqueous layer was treated with sodium sulphite (3 g.) and concentrated hydrochloric acid (25 c.c.) and heated in a boiling water-bath for 30 minutes. After cooling, the yellow solid that separated out was filtered and washed with water; the filtrate furnished some more of the substance on extraction with ether; total yield 0·45 g. When crystallised from glacial acetic acid and subsequently from acetone it separated in the form of bright yellow narrow rectangular plates melting at 255–57°. (Found: C, 59·5; H, 5·2; $C_{20}H_{20}O_9$ requires C, 59·4; H, 4·9%.) It was very sparingly soluble in alcohol, ethyl acetate and acetone and moderately in hot glacial acetic acid. It readily dissolved in aqueous sodium hydroxide (5%) giving a deep red colour which faded considerably on shaking with air. In alcoholic solution with ferric chloride it gave a green colour which quickly changed to deep reddish brown. With *p*-benzoquinone in alcoholic solution a red colour was produced.

The dihydroxy-compound (0.1 g.) was methylated in acetone medium (25 c.c.) with dimethyl sulphate (0·2 c.c.) and potassium carbonate (2 g.). The methyl ether crystallised from a mixture of benzene and petroleum-ether in the form of colourless flat needles melting at 130–31° identical with a sample of 3:5:6:7:8:3′:4′-heptamethoxy-flavone obtained by the method of Seshadri and Venkateswarlu.[2]

5:8-*Dihydroxy*-3:6:7:4′-*tetramethoxy-flavone* (*V*, *R*= *H*):

The required O-tetramethyl-nor-tangeretin (IV, R= H) was obtained by the partial methylation of a synthetic sample of nor-tangeretin as described under quercetagetin.

A stirred solution of 5-hydroxy-3:6:7:4′-tetramethoxy-flavone (IV, R=H) (1 g.) in a mixture of pyridine (20 c.c.) and aqueous potassium hydroxide (1 g. in 25 c.c.) was gradually treated with a solution of potassium persulphate (1·5 g. in 50 c.c.) during the course of two hours. The clear greenish brown solution was kept for 24 hours and just acidified when a pale brown precipitate of the unchanged substance separated out. It was filtered and washed with water. The filtrate was extracted twice with ether and the aqueous layer was heated on a boiling water-bath after the addition

of sodium sulphite (2 g.) and concentrated hydrochloric acid (25 c.c.). The yellow crystalline solid that separated out was filtered and washed with water. The filtrate on extraction with ether provided some more of the substance. Yield 0·4 g. On crystallisation from a mixture of ethyl acetate and petroleum-ether the compound separated out in the form of glistening golden yellow rectangular plates melting at 212–14°. (Found: C, 61·3; H, 5·1; $C_{19}H_{18}O_8$ requires C, 61·0; H, 4·8%).

The above dihydroxy compound (0·2 g.) was refluxed for 6 hours in anhydrous acetone (25 c.c.) with dimethyl sulphate (0·5 c.c.) and potassium carbonate (2 g.). The solvent was distilled off, and the residue treated with water when the methyl ether separated out as a pale brown solid. It was purified by crystallising from a mixture of benzene and petroleum ether when it separated out as colourless rectangular plates melting at 133–34° alone or in admixture with an authentic sample of calycopterin-dimethyl ether.

SUMMARY

It is shown that 5:6:7:8-hydroxy-flavonols (Calycopteretin series) can be made from 5:6:7-hydroxy-flavonols (quercetagetin series) by the nuclear oxidation of the 8-position. Quercetagetin and nor-tangeretin have thus been converted into 6 : 8-dihydroxy-quercetin and calycopteretin in good yields.

REFERENCES

1. Horii — *Br. Chem. Abs.*, 1941, A ii, 331.
2. Seshadri and Venkateswarlu — *Proc. Ind. Acad. Sci.*, A, 1946, **23**, 192.
   Murti, Row and Seshadri .. *Ibid.*, **24**, 233.
   Sastri and Seshadri .. *Ibid.*, **24**, 238.
3. Rao and Seshadri .. *Ibid.*, 1941, **14**, 289.
4. Row and Seshadri .. *Ibid.*, 1946, **23**, 23.
5. Tseng .. *J. C. S.*, 1938, 1003.
6. Nelson .. *J. A. C. S.*, 1934, **56**, 1392.