Nuclear Oxidation of Flavones and Related Compounds. Synthesis of Gardenin.

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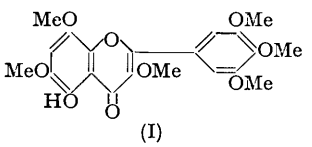
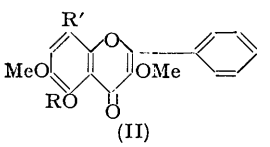
Gardenin has been synthesised from myricetin 3 : 3′ : 4′ : 5′-tetramethyl ether. The important stages are (1) nuclear reduction of the 7-position, (2) *para*-nuclear oxidation of the 8-position with alkaline persulphate, and (3) *ortho*-nuclear oxidation of the 6-position.

Gardenin (I), the yellow crystalline component of Dikamali gum (gum of *Gardenia lucida*), was isolated by Stenhouse and Groves (*J.*, 1877, 552; *Annalen*, 1880, **200**, 311). Its constitution has been established as 5-hydroxy-3 : 6 : 8 : 3′ : 4′ : 5′-hexamethoxyflavone (I) (Bose and Nath, *J. Indian Chem. Soc.*, 1938, **15**, 138; Bose, *ibid.*, 1945, **22**, 233; Balkrishna and Seshadri, *Proc. Indian Acad. Sci.*, 1948, **27**, *A*, 91, 260). It thus belongs to an unusual type of flavonol derivatives and is the only representative known. In the scheme of biogenesis (Balkrishna and Seshadri, *loc. cit.*) it was derived from the fundamental group of 5 : 7-dihydroxyflavonols by processes involving nuclear reduction of the 7-position and nuclear oxidation of the 6- and the 8-position. Illustrating one possible route, the synthesis of the lowest member of the series, 3 : 5 : 6 : 8-tetramethoxyflavone (II*a*) (Balkrishna and Seshadri, *loc. cit.*), involved 5-hydroxy-3 : 6-dimethoxyflavone (II*b*), its *para*-nuclear oxidation with alkaline persulphate (to II*c*), and methylation.



(I)



(II)

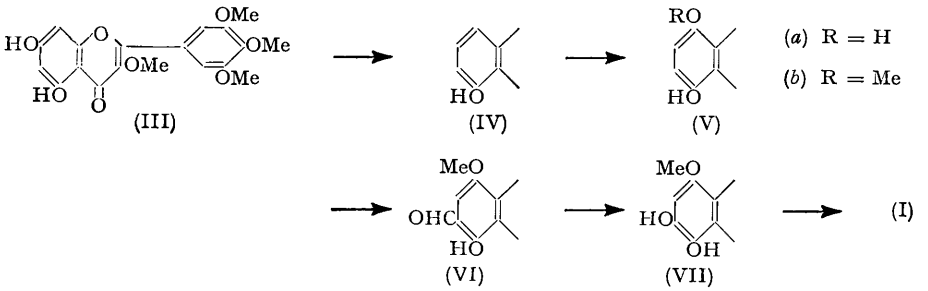
(*a*) R = Me, R′ = OMe

(*b*) R = R′ = H

(*c*) R = H, R′ = OH

Gardenin (I) itself has now been synthesised by an alternative route which involves *ortho*-oxidation of the appropriate 5 : 8-dihydroxyflavone (V*a*) in the 6-position, followed by methylation. Myricetin 3 : 3′ : 4′ : 5′-tetramethyl ether (III) which is readily obtained by Allan–Robinson synthesis (Kalff and Robinson, *J.*, 1925, 181) is the convenient starting point and is subjected to toluene-*p*-sulphonylation in the 7-position and hydrogenolysis with Raney nickel [Ramanathan and Venkataraman, *Proc. Indian Acad. Sci.*, 1953, **38**, *A*, 40; 1954, **39**, *A*, 90; Jain and Seshadri, *J. Sci. Ind. Res.* (*India*), 1953, **12**, *B*, 503; 1954, **13**, *B*, 310]. This method of preparation of 5-hydroxyflavonols is more convenient than the older method employing γ-resacetophenone (Seshadri, Varadarajan, and Venkateswarlu, *Proc. Indian Acad. Sci.*, 1950, **32**, *A*, 250). The present method of nuclear reduction is also in accordance with the scheme of biogenesis. The resulting 5-hydroxy-compound (IV) undergoes persulphate oxidation satisfactorily, to yield the quinol (V*a*) which is a tetramethyl ether of the highest member of the 3-hydroxyprimetin series; the lower members were prepared earlier by nuclear oxidation (Seshadri, Varadarajan, and Venkateswarlu, *loc. cit.*; Ramanathan and Venkataraman, *ibid.*,

1954, **39**, *A*, 90). The quinol (V*a*) is partially methylated and the product (V*b*), which gives all the reactions of a compound containing a free 5-hydroxy-group, is subjected to aldehyde synthesis with hexamine. The yield of the aldehyde (VI) is low (20%) owing to formation of a by-product. The subsequent Dakin oxidation gives a good yield (60%)



of the catechol derivative (VII). A final partial methylation yields gardenin (I) identical with an authentic sample obtained from Dikamali gum.

Experimental

5-Hydroxy-3 : 3′ : 4′ : 5′-tetramethoxy-7-toluene-p-sulphonyloxyflavone.—A suspension of 5 : 7-dihydroxy-3 : 3′ : 4′ : 5′-tetramethoxyflavone (III) (6 g.) in acetone (400 c.c.) containing toluene-*p*-sulphonyl chloride (3·3 g.) and potassium carbonate (8 g.) was refluxed for 4 hr. Acetone was then distilled off, water (300 c.c.) added to the residue, and the solution acidified with dilute hydrochloric acid. The yellow solid was collected, washed with water, and crystallised from acetone, yielding lemon-yellow needles and narrow rectangular plates (6·6 g.) of the *toluene-p-sulphonate*, m. p. 172—173° (Found, in a sample dried at 120° : C, 59·1; H, 4·7. $C_{26}H_{24}O_{10}S$ requires C, 59·1; H, 4·5%). It gives a brown colour with ferric chloride and a sparingly soluble yellow sodium salt with aqueous sodium hydroxide.

5-Hydroxy-3 : 3′ : 4′ : 5′-tetramethoxyflavone (IV).—The above ester (4 g.) in alcohol (500 c.c.) and Raney nickel (12 g.) were stirred in hydrogen at 40° for 1·5 hr. The mixture was filtered and the nickel washed twice with hot alcohol. The filtrate was concentrated to 100 c.c. and treated with potassium hydroxide (3 g.) in a small amount of water, and the solution refluxed for 1 hr. Alcohol was then removed under reduced pressure, and the residue taken up in water and acidified. The precipitate (2 g.) was extracted with cold benzene (3 × 50 c.c.) (undissolved solid S), benzene was distilled off, and the residue crystallised from ethanol, yielding golden-yellow rectangular plates and prisms (0·7 g.), m. p. 131—132°, of the *5-hydroxyflavone* (Found : C, 63·9; H, 5·4. $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·0%). It gave a green ferric reaction and a sparingly soluble yellow sodium salt. The *acetate* crystallised from ethanol as colourless needles, m. p. 179—180° (Found : C, 62·5; H, 5·4. $C_{21}H_{20}O_8$ requires C, 63·0; H, 5·0%).

The undissolved solid (S) (1·2 g.), after crystallisation from pyridine, was identified as the original myricetin tetramethyl ether (III).

5 : 8-Dihydroxy-3 : 3′ : 4′ : 5′-tetramethoxyflavone (V*a*).—A stirred solution of the above 5-hydroxyflavone (3 g.) in pyridine (75 c.c.) and aqueous potassium hydroxide (5 g. in 125 c.c. of water), at 15—20°, was treated dropwise with potassium persulphate (5 g.) in water (250 c.c.) during 3 hr. After 24 hr. at room temperature the deep brown solution was acidified to Congo-red and the unchanged 5-hydroxy-compound (0·6 g.) filtered off, ether-extraction removing the last traces of it. The clear brown aqueous solution was heated with sodium sulphite (4 g.) and concentrated hydrochloric acid (100 c.c.) at 100° for 0·5 hr. It was then cooled and the yellow solid was filtered off and washed with water. The filtrate on ether extraction gave some more of the *quinol*. This crystallised from dilute methanol as orange-yellow rectangular tablets, m. p. 179—180° (1·2 g.) (Found : C, 57·8; H, 5·3; loss at 110°, 4·8. $C_{19}H_{18}O_8,H_2O$ requires C, 58·2; H, 5·1; loss 4·6%. Found, in dried sample : C, 60·7; H, 5·2. $C_{19}H_{18}O_8$ requires C, 61·0; H, 4·8%). The ferric reaction was green, changing to brown.

The *diacetate* crystallised from benzene–light petroleum as colourless rectangular prisms, m. p. 178—179° (Found : C, 60·2; H, 5·3. $C_{23}H_{22}O_{10}$ requires C, 60·3; H, 4·8%).

5-Hydroxy-3 : 8 : 3′ : 4′ : 5′-pentamethoxyflavone (V*b*).—The quinol (2 g.), methyl iodide (2 c.c.), and ignited potassium carbonate (6 g.) in acetone (100 c.c.) were refluxed for 2 hr., then

filtered. Acetone was distilled off and the residue treated with water. The solid product crystallised from ethanol as golden-yellow prismatic needles and rods (1·9 g.), m. p. 147—148°, giving a stable green ferric reaction in ethanol (Found: C, 61·8; H, 4·9. $C_{20}H_{20}O_8$ requires C, 61·9; H, 5·1%).

The *acetate* formed colourless needles (from ethanol), m. p. 178—180° (Found: C, 61·2; H, 5·2. $C_{22}H_{22}O_9$ requires C, 61·4; H, 5·1%).

5-*Hydroxy*-3 : 8 : 3′ : 4′ : 5′-*pentamethoxyflavone*-6-*aldehyde* (VI).—A solution of the above 5-hydroxy-compound (1 g.) and hexamine (3 g.) in glacial acetic acid (20 c.c.) was heated on a boiling-water bath for 6 hr., then boiling hydrochloric acid (1 : 1; 20 c.c.) was added and heating continued for 0·5 hr. The cooled mixture was diluted with water, and the yellow precipitate (0·6 g.) filtered off. Extraction of this with hot alcohol (150 c.c.) left a residue (A). Removal of alcohol from the extract gave a brownish-yellow product (0·2 g.) which crystallised from ethyl acetate containing a few drops of chloroform as brownish-yellow prismatic needles and rods, m. p. 212—214° (Found: C, 60·5; H, 5·0. $C_{21}H_{20}O_9$ requires C, 60·6; H, 4·8%). This *aldehyde* gives a deep olive-green ferric reaction in ethanol and a 2 : 4-dinitrophenylhydrazone as brown-red plates (from ethanol), m. p. 268—270°.

The insoluble portion (A) (0·4 g.) crystallised from chloroform as pale yellow hairy needles, m. p. 277—279°, and did not give any ferric reaction or 2 : 4-dinitrophenylhydrazone.

5 : 6-*Dihydroxy*-3 : 8 : 3′ : 4′ : 5′-*pentamethoxyflavone* (VII).—A cooled (20°) solution of the above flavone-aldehyde (80 mg.) in pyridine (4 c.c.), 0·5N-sodium hydroxide (0·6 c.c.), and water (3 c.c.) was treated dropwise with hydrogen peroxide (0·3 c.c.; 6%) during 15 min. The solution, initially deep brownish-red, became pale yellow. After 2 hr. the mixture was acidified with ice-cold dilute hydrochloric acid, and the yellow precipitate was filtered off. The *dihydroxyflavone* crystallised from chloroform–methanol as deep yellow prisms (55 mg.), m. p. 200—202° (Found: C, 59·8; H, 5·3. $C_{20}H_{20}O_9$ requires C, 59·4; H, 5·0%). Its ferric reaction was brown, deepening with excess of reagent.

Gardenin (I).—The flavone (VII) (40 mg.) was refluxed with excess of methyl iodide and potassium carbonate in acetone for 1·5 hr. The product was crystallised from ether–light petroleum and finally from dilute alcohol and was obtained as golden-yellow needles, m. p. and mixed m. p. 163—165°. The colour reactions with ferric chloride and nitric acid (*d* 1·2) were identical with those for authentic gardenin.

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