

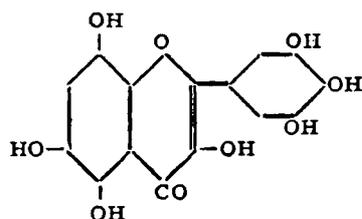
SYNTHESIS AND STUDY OF 5: 6: 8-HYDROXY FLAVONOLS

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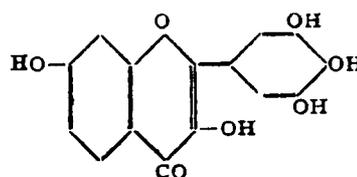
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As already pointed out¹ nor-gardenin (I) is characterised by an extraordinary lack of colour effect in alkaline solutions and this forms an important contrast to the marked colour changes exhibited by the isomeric flavonols, hibiscetin and 6-hydroxymyricetin and even by the much simpler compound, robinetin (II).



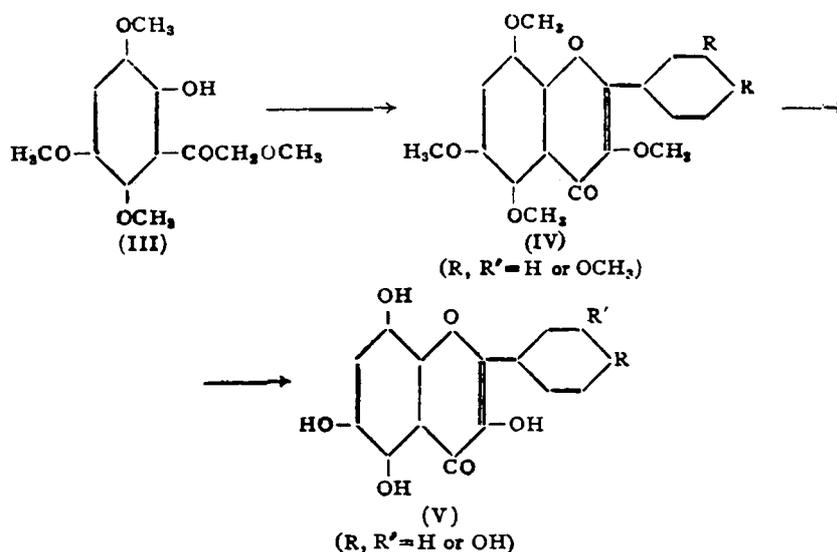
(I)



(II)

This was attributed mainly to the absence of the 7-hydroxyl group in nor-gardenin. It has therefore been felt necessary to prepare the analogues of nor-gardenin in order to have more examples. Further, there is also the possibility of their being discovered in nature in future. Then the recorded properties of the synthetic compounds will render their identification more easy. Their total synthesis is very difficult. The only available method was used in the synthesis of 3:5:6:8-tetramethoxy-flavone and this was described in an earlier publication.¹ The simpler alternative would require the synthesis of ω -3:5:6-tetramethoxy-2-hydroxy-acetophenone (III) and condensing it with the anhydrides and sodium salts of various acids. But no method has so far been developed for the synthesis of this ketone. However, it could be readily obtained by the alkali fission of methyl gardenin and the yield is quite high being about 50% of the weight of methyl gardenin taken. Hence this fission ketone has been employed for the condensation by the Allan-Robinson method. The synthesis using benzoic anhydride and sodium benzoate was described in the earlier paper.¹ The tetramethoxy compound (IV, R = R' = H) was found to be identical with the one obtained from 3:5:6-trihydroxy flavone by nuclear oxidation. The two have now

been independently demethylated and the samples of the tetrahydroxy compound (V, R = R' = H) thus produced compared. They are found to be identical in every respect. The synthesis has been further carried out using the anhydrides and sodium salts of anisic and veratric acids. Just as in the partial synthesis of gardenin and in the condensation using benzoic anhydride and sodium benzoate even in these two cases there is partial demethylation in the course of the reaction. But the crude products have been directly demethylated or methylated in order to obtain the penta- (V, R = OH, R' = H) or hexa- (V, R = R' = OH) hydroxy-compounds and their fully methylated derivatives (IV).



The melting points of the four flavonols of this series are embodied in the table given below. The following remarks could be made on the data. There is a gradual rise in the melting points of the hydroxy compounds with the increase in the number of hydroxyl groups whereas in the case of the methoxy compounds there is a maximum in the second member and then a decrease in the melting point as the number of methoxyls increases. The colour reactions are just the same for all the members of this group and the variation in the number of hydroxyl groups in the side phenyl nucleus seems to have absolutely no effect. These hydroxy compounds differ markedly from the isomeric 5:6:7- and 5:7:8-hydroxy flavonols. Thus there seems to be sufficient confirmation of the idea that the alkali colour reaction is very much dependent on the presence or absence of a hydroxyl group in this position. Another noteworthy feature is that Bargellini's test using sodium amalgam and alcohol is uniformly negative. The characteristic green flocks

given by the 5:6:7-hydroxy-flavones is not given. Even the small variation in the arrangement of the hydroxyl groups from 5:6:7- to 5:6:8-causes this difference. It has already been pointed out that even 5:6:7:8-hydroxyl compounds² do not respond to this test though there is only an addition of a hydroxyl group, the original 5:6:7-arrangement being kept up. There is therefore considerable amount of specificity in this reaction. With regard to the reduction using magnesium and hydrochloric acid in alcoholic solution the methyl ethers give considerably brighter colours than the corresponding hydroxy compounds.

	Tetra-hydroxy flavone	Penta-hydroxy flavone	Hexa-hydroxy flavone	Hepta-hydroxy flavone (norgardenin)
M.P. of the hydroxy compounds ..	218-20°	258-60°	275-77°	320°
M.P. of the methyl ethers ..	118-19°	142-44°	130-32°	116-17°

EXPERIMENTAL

2-Hydroxy- ω -3:5:6-tetramethoxy-acetophenone required for the following experiments was obtained by the fission of methyl gardenin using absolute alcoholic potash as already described.¹ It was in the form of bright yellow rectangular plates, melting at 88-89°.

3:5:6:8-Tetrahydroxy-flavone (V , $R = R' = H$)

The condensation of the ketone with benzoic anhydride and sodium benzoate has already been described.¹ The crude condensation product (0.5 g.) was dissolved in acetic anhydride (2 c.c.) and hydriodic acid (10 c.c.; d., 1.7) added with cooling under the tap. The mixture was gently boiled for one hour. After cooling, it was diluted with water and saturated with sulphur dioxide. The yellow solid that separated out was filtered and crystallised from acetic acid. It was obtained as bright yellow small prisms melting at 218-20°. (Found: C, 63.1; H, 3.8; $C_{15}H_{10}O_6$ requires C, 62.9; H, 3.5%.) The following reactions were carried out using an alcoholic solution of the substance. Ferric chloride gave first a green colour which changed to blue immediately followed by a greenish-blue precipitate. Magnesium and hydrochloric acid produced a red colour, *p*-benzoquinone a reddish-brown colour and sodium amalgam an immediate brown precipitate. The substance dissolved in aqueous sodium hydroxide, sodium carbonate and bicarbonate. In the first case a reddish-brown solution was first formed which changed to pale brown in the course of 5 minutes; in the second, a bright yellow solution was first produced which rapidly changed

to brown and in the last, there was first a greenish-yellow solution which changed to yellow.

Condensation of the ketone with anisic anhydride and sodium anisate

An intimate mixture of the ketone (1.0 g.) with anisic anhydride (10 g.) and sodium anisate (3 g.) was heated at 175–80° under reduced pressure for three hours. The product was dissolved in boiling alcohol (50 c.c.) and a 50% solution of potassium hydroxide (6 g.) was slowly added during 20 minutes while the solution was refluxing. The alcohol was removed under reduced pressure. The residue was dissolved in water and the aqueous solution was filtered. On saturating the aqueous filtrate with carbon dioxide a bright yellow solid separated out. It was extracted with ether. The ether solution when concentrated deposited bright yellow needles, giving an olive-green ferric chloride colour. Yield, 0.6 g.

3:5:6:8:4'-Pentahydroxy-flavone (V, R = OH, R' = H)

The above condensation product (0.4 g.) was demethylated using hydriodic acid and acetic anhydride as already described for a similar case. The penta-hydroxy compound crystallised from acetic acid as bright yellow prisms melting at 258–60°. (Found: C, 59.3; H, 3.1; $C_{15}H_{10}O_7$ requires C, 59.6; H, 3.3%.) The colour reactions of this compound were just the same as those of the tetrahydroxy compound described earlier in this paper.

3:5:6:8:4'-Pentamethoxy-flavone (IV, R = OCH₃, R' = H)

The crude condensation product (0.2 g.) was dissolved in dry acetone (25 c.c.) and treated with dimethyl sulphate (0.8 c.c.) and anhydrous potassium carbonate (8 g.). The solution was refluxed for 30 hours and the potassium salts were filtered off. The acetone filtrate was concentrated and diluted with water when a colourless solid was obtained. It was filtered and crystallised from alcohol. It was thus obtained as colourless needles melting at 142–44°. (Found: C, 64.7; H, 5.1; $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4%.) With alcoholic ferric chloride it did not give any colour and was insoluble in aqueous alkali. With magnesium and hydrochloric acid it gave a deeper red colour than the corresponding hydroxy-compound.

Condensation of the ketone with veratric anhydride and sodium veratrate

This was carried out using the ketone (1.0 g.), veratric anhydride (10 g.) and sodium veratrate (5 g.) according to the procedure already described. The crude product was obtained as yellow needles which gave an olive green ferric chloride colour. Yield, 0.6 g.

3:5:6:8:3':4'-Hexahydroxy-flavone (V, R = R' = OH)

The above condensation product (0.4 g.) was demethylated using hydriodic acid and acetic anhydride. The hexahydroxy-flavone crystallised from acetic acid as bright yellow prisms melting at 275–77°. (Found: C, 56.0; H, 3.5; C₁₅H₁₀O₈ requires C, 56.2; H, 3.2%.) The colour reactions of this compound also were the same as those of the compounds of this series already described.

3:5:6:8:3':4'-Hexamethoxy-flavone (IV, R = R' = OCH₃)

The crude condensation product (0.2 g.) was methylated in dry acetone medium using anhydrous potassium carbonate and dimethyl sulphate, and following the procedure described already. The methyl ether crystallised from alcohol as colourless needles melting at 130–32°. (Found: C, 62.5; H, 5.2; C₂₁H₂₂O₈ requires C, 62.7; H, 5.5%.) It did not give any colour with alcoholic ferric chloride and was insoluble in aqueous sodium hydroxide. With magnesium and hydrochloric acid it gave a deeper red colour than the corresponding hydroxy compound.

SUMMARY

In an earlier paper it was remarked that the colour reactions of nor-gardenin were rather extraordinary. Other flavonols belonging to the 5:6:8-hydroxy series and their methyl ethers have now been prepared using the fission ketone from methyl gardenin, and their properties studied. Their colour reactions resemble those of nor-gardenin and methyl gardenin closely. In general the hydroxy-flavonols of this series exhibit reactions with alkaline buffer solutions differing markedly from their isomers belonging to the 5:7:8- or 5:6:7- series thus emphasising the importance of the 7-hydroxyl for this purpose.

REFERENCES

1. Balakrishna and Seshadri .. *Proc. Ind. Acad. Sci.* A, 1948, 27, 91.
2. Seshadri and Venkateswarlu .. *Ibid.*, 1946, 23, 192.