

8-HYDROXY-GALANGIN

BY P. RAMACHANDRA RAO AND T. R. SESHADRI

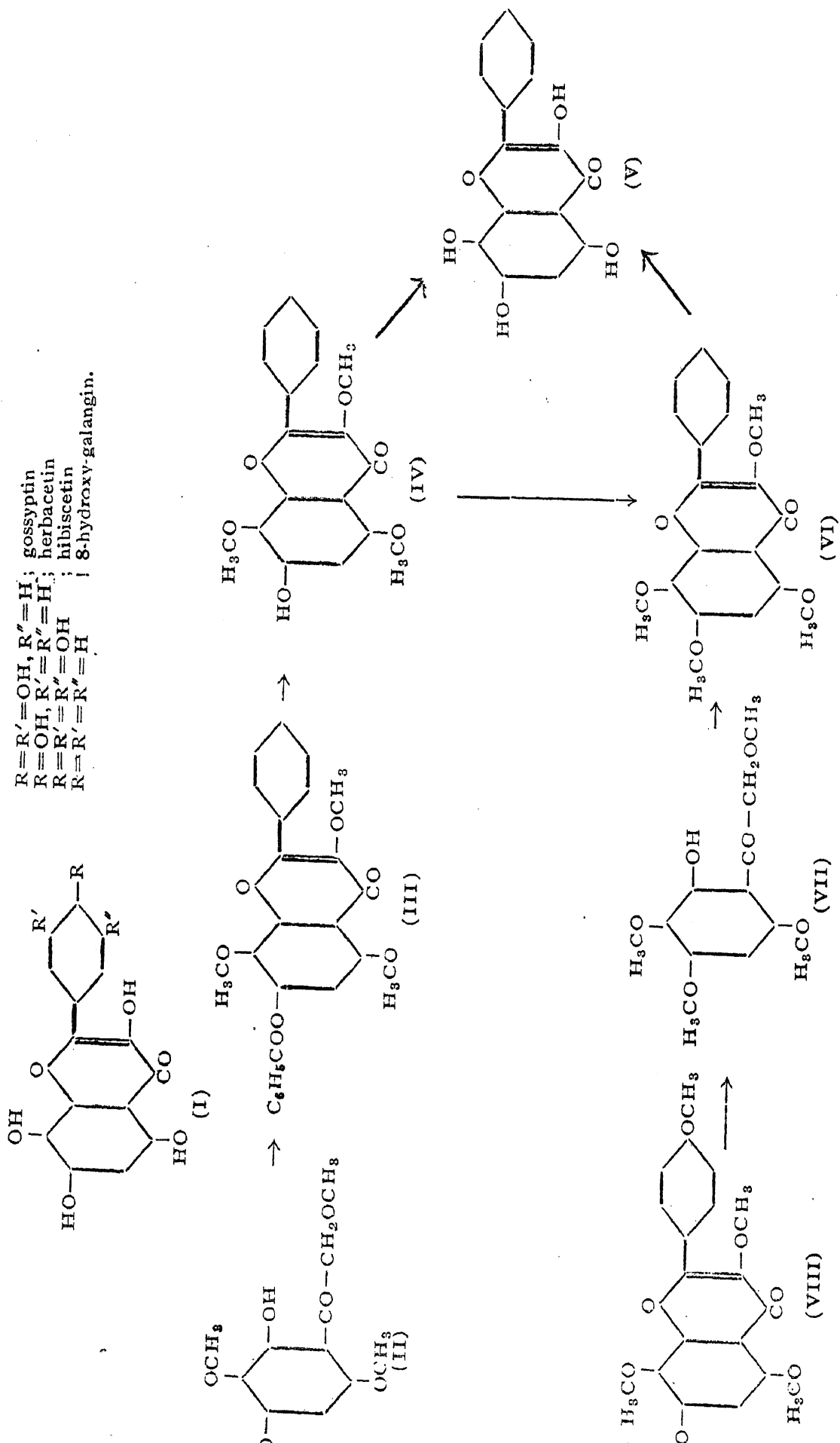
(From the Department of Chemistry, Andhra University)

Received August 22, 1945

AMONG the flavonols having the 5:7:8-orientation of hydroxyl groups, gossypetin was the first to be discovered and studied. It has been found in the Indian and Egyptian cotton flowers and in the flowers of *Hibiscus sabdariffa*. More recently herbacetin and hibiscetin have been isolated. The former is present in the flowers of *Gossypium herbaceum* and *Thespesia populnea* both free and as glucoside. Hibiscetin has so far been found to occur only in *Hibiscus sabdariffa*. The lowest member of the series, 8-hydroxy-galangin has not yet been isolated from natural products. It may however, be expected to occur and hence a study of this substance and of its derivatives is reported in this paper.

The synthesis of hydroxy-galangin has been effected on the same lines as the synthesis of gossypetin and herbacetin by Robinson and his co-workers,¹ but the required ketone, 2:4-dihydroxy- ω -3:6-trimethoxyacetophenone (II) is made by the simplified procedure of Rao, Rao and Seshadri² as described in connection with the synthesis of hibiscetin. It has been possible to isolate the 7-benzoyloxy derivative (III) as product of the Allan-Robinson condensation of the above ketone with benzoic anhydride and sodium benzoate. Subsequent hydrolysis yields 7-hydroxy-3:5:8-trimethoxy-flavone (IV). Demethylation of (IV) produces the tetrahydroxy flavone, 8-hydroxy-galangin (V) and methylation of (IV) forms the tetramethyl ether (VI). The tetramethyl ether has also been obtained directly by repeating the above condensation using 2-hydroxy- ω :3:4:6-tetramethoxy-acetophenone (VII), also called gossypetol tetramethyl ether⁷ since it was first obtained by the alkaline fission of hexamethyl gossypetin. We have now been able to carry out the fission of pentamethyl herbacetin³ (VIII) using sufficient quantities and isolate this ketone in good yield. This reaction is an important support for the constitution of herbacetin and could not be done earlier due to lack of material. It may be mentioned here that herbacetin is best methylated by means of dimethyl sulphate and potassium carbonate in anhydrous acetone medium.

The new flavonol (V) has the characteristic properties of the group. When treated with *p*-benzo-quinone or quinhydrone it gives the gossypetone reaction forming a reddish brown quinone. It also exhibits prominent



colour changes with alkaline buffer solutions. In regard to these colours there is a marked gradation from the lowest to the highest member of this group of flavonols. With hydroxy-galangin the violet colour is prominent and it diminishes in herbacetin⁴ and gossypetin⁵ and is absent in hibiscetin.⁶ On the other hand, the pure and deep blue tone intensifies as the series is ascended. The stability of the flavonols in the solid state diminishes with increasing number of hydroxyl groups. Hydroxy-galangin retains its golden yellow colour almost indefinitely whereas hibiscetin becomes dark in a few weeks. A similar sequence is found in the melting points of the flavonols and of their important derivatives as shown in the following table :—

	Flavonol	Methyl ether	Acetate
Hydroxy-galangin ..	231-33°	155-56°	169-70°
Herbacetin ..	281-83°	157-58°	192-93°
Gossypetin ..	310° (decomp.)	170-72°	228-30°
Hibiscetin ..	350° (decomp.)	194-96°	242-44°

EXPERIMENTAL

2: 4-Dihydroxy- ω -3: 6-trimethoxy acetophenone (II).—This was prepared by the modified method of Rao, Rao and Seshadri.²

7-Benzoyloxy-3: 5: 8-trimethoxy flavone (III).—2: 4-Dihydroxy- ω -3: 6-trimethoxy acetophenone (II) (2 g.) was intimately mixed with sodium benzoate (10 g.) and benzoic anhydride (20 g.) and the mixture was heated under reduced pressure for four hours in an oil-bath at 175-80°. The mixture gradually shrank and partly melted down into a liquid. The reaction product was dissolved in boiling alcohol (150 c.c.), sodium hydroxide (6.5 g.) required just to neutralize the unreacted benzoic anhydride, was dissolved in 15 c.c. of water and this was added to the above boiling solution in small quantities during the course of 20 minutes. The mixture was then boiled under reflux for half an hour, and the solvent subsequently removed under reduced pressure. The residue, consisting essentially of the benzoyloxy compound, benzoic acid and its potassium salt, was macerated with dilute sodium carbonate solution. By this treatment benzoic acid and its salt went into solution leaving behind the benzoyloxy compound. It was filtered and recrystallised from a mixture of alcohol and acetic acid. It was thus obtained as colourless rhombic prisms melting at 185-87°, sintering a few degrees earlier. The yield was about 1.5 grams. (Found in the air-dried sample: C, 68.1; H, 5.1; C₂₅H₂₀O₇, $\frac{1}{2}$ H₂O requires C, 68.0; H, 4.8%.)

7-Hydroxy-3: 5: 8-trimethoxy flavone (IV).—The benzoyl compound (III) was dissolved in boiling alcohol (100 c.c.) and treated with 10% potassium

hydroxide (10 c.c.) in small quantities during the course of 20 minutes. The mixture was then boiled under reflux for half an hour. The clear solution which was blue to litmus was cooled and the solvent removed under reduced pressure. The residue was treated with 50 c.c. of water and any undissolved impurity was removed by filtration. The clear alkaline solution was saturated with carbon dioxide when a crystalline yellow substance separated out in good yield. It was recrystallised from glacial acetic acid. When the crystallisation was carried out quickly, the substance came out as yellow rectangular plates and flat needles; by slow crystallisation, however, rectangular prisms were obtained. The melting point was 236–38°. Yield 0.5 g. The substance was soluble in alkali and gave no characteristic colour with ferric chloride. (Found in the air-dried sample: C, 64.1; H, 5.3; loss on drying at 120° *in vacuo* for 2 hours: 3.1; $C_{18}H_{16}O_6 \frac{1}{2} H_2O$ requires C, 64.1; H, 5.1; loss on drying, 2.7%.)

8-Hydroxy-Galangin (3:5:7:8-Tetrahydroxy flavone) (V).—7-Hydroxy-3:5:8-trimethoxy flavone (IV) (0.5 g.) was dissolved in acetic anhydride (2.5 c.c.) and treated with hydriodic acid (10 c.c.) of 1.7 density. The mixture was boiled under reflux for half an hour. After dilution with an equal amount of water, sulphur dioxide was passed through the solution in order to remove iodine. A yellow solid separated out in good yield. Direct crystallisation was not satisfactory. So the crude product was dissolved in dry ether and the solution treated with petroleum ether. Some brown amorphous impurities were first precipitated and were removed. Further addition of petroleum ether gave hydroxy-galangin as a bright yellow crystalline solid. It was finally crystallised from alcohol when it came out as fibrous needles melting at 231–33° sintering a few degrees earlier. (Found in the air-dried sample: C, 62.8; H, 3.9; $C_{15}H_{10}O_6$ requires C, 62.9; H, 3.5%.) There was no loss on drying at 120° *in vacuo* for two hours.

An alcoholic solution of the flavonol gave a deep red precipitate with neutral lead acetate and a brownish red colour with ferric chloride. The substance dissolved in concentrated sulphuric acid to form a yellow solution without fluorescence and dissolved in dilute alkali producing a purple solution which rapidly became yellowish-green on shaking.

The colour reactions of the flavonol in alkaline buffer solutions were as described below:

p_H 8.6. Rapidly dissolved to give a deep yellow solution. Slowly changed to violet (2 minutes) and then to bluish violet (10 minutes). The colour was stable for more than two hours. After twenty-four hours, the solution was colourless.

p_H 9.8. Dissolved immediately yielding a yellow solution which changed to violet and then to violet-blue within five minutes. The colour was fairly stable for two hours. After twenty-four hours the solution was colourless.

p_H 10.4. The initial yellow solution quickly changed to brown violet and then to violet. Within a minute, the solution was deep violet-blue which was stable for two hours; it was colourless after twenty-four hours.

p_H 11.0. Quick succession of changes: yellow, brown-violet, violet, deep violet-blue within half a minute. The colour was bluer than before. Stable for two hours but faded away within 24 hours.

By the action of *p*-benzoquinone in alcoholic solution the quinone derivative was obtained as a deep reddish brown solid which did not melt below 300° C. The tetra-acetyl derivative of the flavonol crystallised from alcohol in the form of colourless prismatic needles and melted at 169–70°.

7-Acetoxy-3:5:8-trimethoxyflavone 7-Hydroxy-3:5:8-trimethoxyflavone (IV) (0.2 g.) was acetylated using acetic anhydride and anhydrous sodium acetate. The acetyl derivative was sparingly soluble in alcohol. It crystallised from acetic acid as needles melting at 155–56°. (Found in the air-dried sample: C, 62.0; H, 5.5; loss on drying at 120° *in vacuo* for 2 hours, 4.2; $C_{20}H_{18}O_7$, H_2O requires C, 61.9; H, 5.2; loss on drying, 4.6%.)

3:5:7:8-Tetramethoxy flavone (VI).—7-Hydroxy-3:5:8-trimethoxy flavone (IV) (0.2 g.) was dissolved in 20% sodium hydroxide (5 c.c.) and was treated with dimethyl sulphate (0.5 c.c.) added in drops with vigorous shaking. During this 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 separated out completely. When recrystallised from dilute acetic acid, it was obtained as colourless woolly needles melting at 156–58° with sintering at about 100° (dehydration). (Found in air-dried sample: C, 60.5; H, 6.1; OCH_3 , 31.9; $C_{19}H_{18}O_6$, $2H_2O$ requires C, 60.3; H, 5.8 and OCH_3 , 32.8%. Found in the sample dried at 120° *in vacuo*: C, 66.2; H, 5.7; $C_{19}H_{18}O_6$ requires C, 66.7; H, 5.3%.)

Pentamethyl Herbacetin (VIII).—Herbacetin (2 g.) was dissolved in anhydrous acetone (50 c.c.); the solution was treated with anhydrous potassium carbonate (25 g.) and dimethyl sulphate (8 c.c.) and boiled under reflux for 30 hours. A further quantity of dimethyl sulphate (6 c.c.) was added in small quantities during the first 24 hours. The mixture was finally filtered under suction while still hot and the residue was washed with a small quantity of hot anhydrous acetone. The filtrate was concentrated;

on the addition of excess of water the concentrate gave rise to a bulky precipitate of the methylated flavonol. It was filtered and recrystallised from dilute alcohol. Its crystal structure (fibrous needles) and melting point (156–58°) were identical with the pentamethyl ether already described.

2-Hydroxy- ω -3: 4: 6-tetramethoxy acetophenone (Gossypetol-tetramethyl ether) (VII).—Pentamethyl herbacetin (VIII) (1 g.) was treated with absolute alcoholic potash (2 g. of potash in 30 c.c. of absolute alcohol) and boiled under reflux on a water-bath for about six hours. As much of the alcohol as possible was then removed by distillation, the residue dissolved in water and the solution acidified with excess of dilute sulphuric acid. The product was then ether-extracted and the ether solution was washed repeatedly with 5% sodium bicarbonate solution till no more acid could be extracted. The solvent was then distilled off and the solid obtained was recrystallised from dilute alcohol. It appeared as colourless flat needles melting at 115–16°. Gossypetol-tetramethyl ether according to Perkin⁷ has the same crystal structure (needles) and melting point 115–16°.

The sodium bicarbonate washings were acidified and the acid that precipitated out was recrystallised from alcohol. It was found to be identical with anisic acid.

The ketone (gossypetol-tetramethyl ether) on condensation with benzoic anhydride and sodium benzoate gave rise to 3:5:7-8-tetramethoxy-flavone identical with the sample prepared by the methylation of 7-hydroxy-3:5:8-trimethoxy-flavone.

SUMMARY

8-Hydroxy-galangin, the lowest member of the gossypetin series of flavonols, has been prepared and its properties and reactions compared with the other members. Its important derivatives are described. The tetramethyl ether has been obtained by two methods, one of which is the direct condensation of gossypetol-tetramethyl ether, obtained by the fission of herbacetin pentamethyl ether, with benzoic anhydride and sodium benzoate.

REFERENCES

1. Baker, Nodzu and Robinson *J. C. S.*, 1929, 74.
Goldsworthy and Robinson *Ibid.*, 1937, 46.
2. Rao, Rao and Seshadri .. *Proc. Ind. Acad. Sci.*, A, 1943, 19, 88.
3. Rangaswami, Rao and Seshadri *Ibid.*, 1939, 9, 133 ;
Rao and Seshadri .. *Curr. Sci.*, 1939, 6, 255.
4. Neelakantam and Seshadri *Proc. Ind. Acad. Sci.*, A, 1937, 5, 362.
5. ———, ——— and Rao .. *Ibid.*, 1935, 2, 492.
6. Rao and Seshadri .. *Ibid.*, 1942, 15, 150.
7. Perkin .. *J. C. S.*, 1913, 653.