

NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

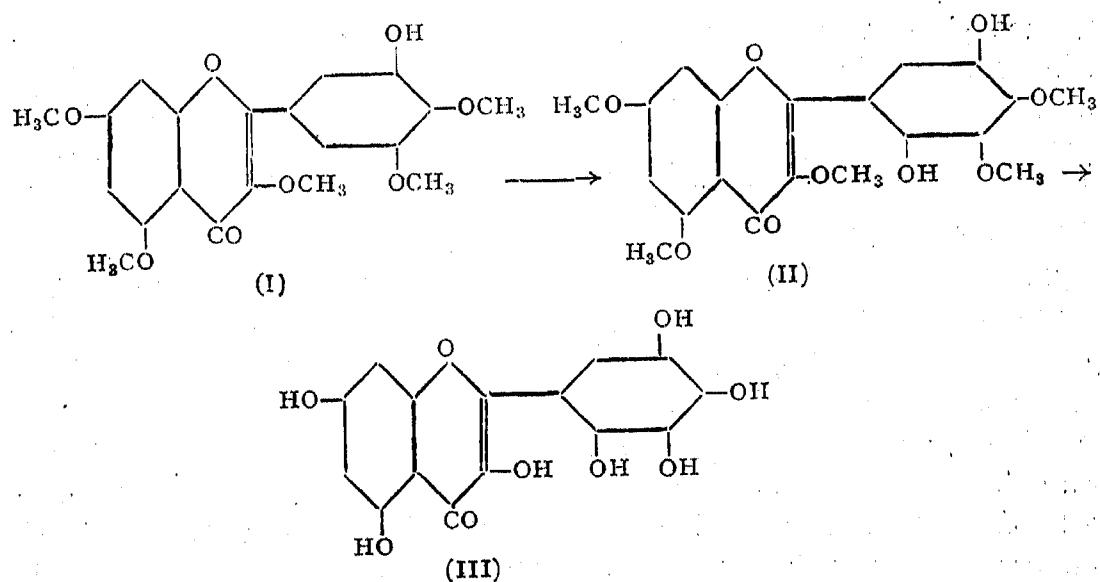
Part XLI. A Study of 2':5'-Hydroxy-Flavonols

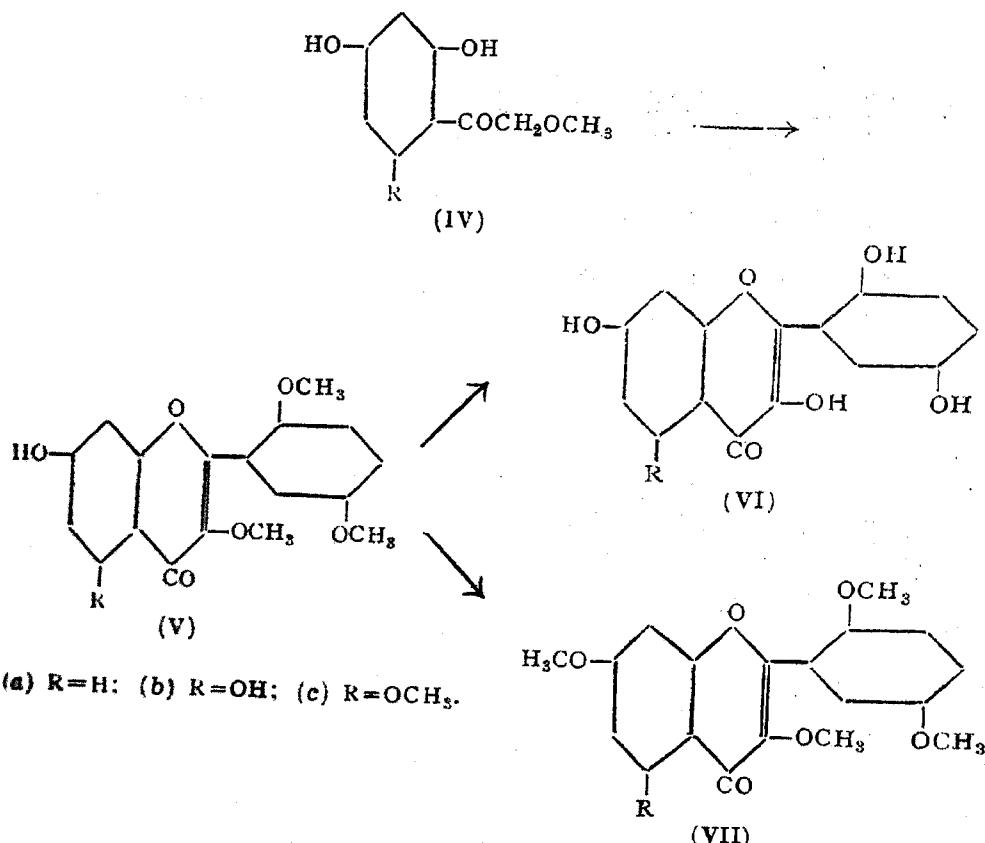
By J. M. SEHGAL AND T. R. SESHADRI, F.A.Sc.

(From the Department of Chemistry, Delhi University, Delhi)

(Received September 22, 1952)

IN Part XXXIV¹ the first example involving para-nuclear oxidation in the side phenyl nucleus of the flavone structure was described. 3':5:7:4':5'-pentamethoxy flavone (I) obtained from the glucoside cannabiscitrin was oxidised with persulphate to the 3':6'-dihydroxy compound (II) and by subsequent demethylation the corresponding hepta-hydroxy flavone was secured (III). It was noticed that in regard to the alkali colour reactions the introduction of the para-dihydroxy grouping did not produce any marked difference as in similar cases involving the condensed benzene ring. In order to get more information on the influence of the dihydroxyl groups in the side phenyl nucleus simpler examples have now been prepared. These are 3:7:2':5'-tetra-hydroxy flavone (VI a) and 3:5:7:2':5'-penta-hydroxy flavone (VI b). They have been obtained by flavone synthesis in which ω -methoxy resacetophenone (IV a) and ω -methoxy-phloroacetophenone (IV b) are condensed with the anhydride and the sodium salt of gentisic acid dimethyl ether.



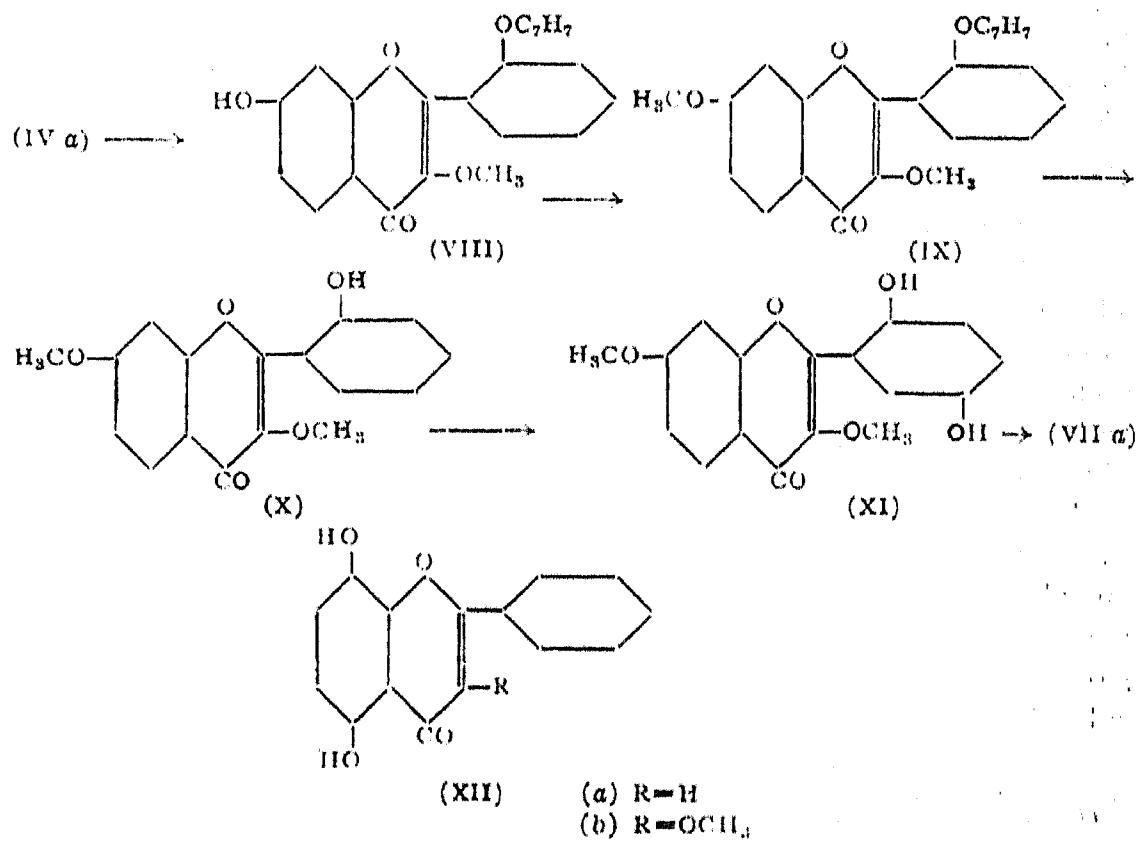


The resorcinol derivative (VII a) has also been independently prepared using the method of nuclear oxidation. The stages are as follows:

ω-Methoxy resacetophenone (IV a) is condensed with the anhydride of 2-benzyloxy benzoic acid and its sodium salt. The resulting 7-hydroxy-3-methoxy-2'-benzyloxy flavone (VIII) is methylated and subsequently debenzylated using acetic acid and hydrochloric acid. 3:7-Dimethoxy-2'-hydroxy flavone (X) obtained thereby undergoes para-nuclear oxidation with potassium persulphate yielding the quinol (XI) which, on methylation, yields 3:7:2':5'-tetramethoxy flavone identical with the sample obtained by the direct flavone synthesis.

A study of the colour reactions of the new compounds is of interest. Compound (X) is the first example obtained so far having a free hydroxyl group only in the 2'-position. It does not give the ferric chloride colour thus ruling out the existence of chelation between the hydroxyl and the pyrone oxygen. A lone hydroxyl in the 8-position gives a prominent colour with alcoholic ferric chloride.³ That given by a 5-hydroxyl which is chelated with the CO group is well known. Even the quinol (XI) is very unimpressive in its colour reactions as compared with primetin³ (XII a) or 3-methoxy primetin⁴ (XII b). It gives no colour with ferric chloride and with

alkali only a light yellow. Its oxidation with *p*-benzoquinone to give a red coloured product is very slow. The tetra- and penta-hydroxy flavones (*VI a*, *VI b*) do not give prominent colours in alkaline solution as is common with flavonols having the quinol unit in the condensed benzene ring (e.g., 3-hydroxy primetin),⁴ but they give red colour with excess of ferric chloride and benzoquinone. It is remarkable that these compounds and their derivatives do not give any detectable fluorescence. The 2':5' combination of hydroxyl and methoxyl groups seems to inhibit fluorescence emission.



EXPERIMENTAL

2:5-Dimethoxy benzoic acid

2:5-Dihydroxy benzoic acid required for this purpose was prepared in about 40% yield by the nuclear oxidation of salicylic acid with potassium persulphate in alkaline medium. If sodium persulphate is used in excess and the volume of the solution kept down as low as possible the yield of gentisic acid can be raised considerably (60%). It crystallised from water as colourless needles melting at 200-01°. It gives a deep blue colour with alcoholic ferric chloride. Its methylation to dimethyl ether was carried out earlier by Mauthner.⁵ The following method is more convenient and gives a good yield of a pure product.

Gentisic acid (5 g.) was refluxed in dry acetone (250 c.c.) solution with ignited potassium carbonate (25 g.) and freshly distilled dimethyl sulphate (17 c.c.) for a period of 50 hours. The acetone solution was filtered and the potassium salts washed with a small quantity of hot acetone. On distilling off the solvent from the filtrate a brownish yellow viscous oil was left which was taken in ether and washed twice with 2% cold aqueous sodium hydroxide to free it from any monomethyl ether. The oily mass obtained after the evaporation of ether was hydrolysed by refluxing it with 10% aqueous sodium hydroxide for 2 hours. The brownish red solution was filtered and acidified when the dimethyl ether of gentisic acid separated out as a pale brown solid. It crystallized from hot water as colourless needles melting at 76°; yield 5.1 g. It did not give any colour with alcoholic ferric chloride.

Anhydride of 2:5-Dimethoxy benzoic acid

Dry 2:5-Dimethoxy benzoic acid (20 g.) was taken in anhydrous ether (75 c.c.) in a 500 ml. conical flask and dry pyridine (8.6 c.c.) added to it. The contents were cooled to 0° C. and a solution of thionyl chloride (4 g.) in dry ether was slowly added in small lots with frequent shaking during the course of 30 minutes maintaining the temperature below zero during the addition. The flask was left in the refrigerator overnight, the solid mass filtered and triturated successively with ice-cold dilute hydrochloric acid, ice-cold 5% sodium bicarbonate solution and cold water. It was finally washed thoroughly with water to remove traces of sodium bicarbonate. The solid anhydride was dried by pressing between folds of filter-paper and keeping in a vacuum desiccator for a few days. The dry anhydride was crystallized from dry ethyl acetate and petroleum ether mixture when it appeared as colourless needles and rectangular prisms melting at 97-8° (Found: C, 62.9; H, 5.4. $C_{10}H_{18}O_7$ requires C, 62.4; H, 5.2%).

7-Hydroxy-3:2':5'-trimethoxy flavone (Va)

α -Methoxy resacetophenone (2 g.) was intimately mixed with gentisic anhydride (16 g.) and sodium gentisate (4 g.) and heated in an oil-bath at 180-85° for 4 hours under reduced pressure. The dark viscous mass thus obtained was left overnight and refluxed for 30 minutes with 7% alcoholic potash (5.3 g. in 80 c.c.). Most of the alcohol was removed by heating over a steam-bath under vacuum, the residue dissolved in water and the dark brown solution was filtered and saturated with carbon dioxide. It was extracted with ether, the ether extract dried over anhydrous sodium sulphate and the solvent distilled off. The reddish yellow mass thus obtained was crystallized from ethyl acetate-petroleum ether mixture. The compound came out in the form of pale yellow wedge-shaped crystals melting

at 240–42°; yield 1.8 g. (Found: C, 66.1, H, 5.1. $C_{18}H_{16}O_6$ requires C, 65.9; H, 4.9%). It did not develop any colour with alcoholic ferric chloride, gave a pale yellow solution with 5% sodium hydroxide and on reduction with magnesium and hydrochloric acid developed a red colour. With concentrated sulphuric acid it showed no fluorescence.

3:7:2':5'-Tetramethoxy flavone (VII a)

The above 7-hydroxy compound (0.5 g.) was dissolved in anhydrous acetone (75 c.c.) and boiled with dimethyl sulphate (0.6 c.c.) and anhydrous potassium carbonate (6 g.) for 8 hours. The tetramethoxy flavone initially came out as a viscous oil which gradually solidified on cooling and scratching with a glass rod. It crystallized from ethyl acetate and petroleum ether mixture as colourless flat needles and rectangular rods melting at 169–70°; yield, 0.41 g. (Found: C, 66.9; H, 5.3. $C_{19}H_{18}O_6$ requires C, 66.7; H, 5.3%). It was insoluble in cold dilute sodium hydroxide, gave no colour with aqueous ferric chloride and on reduction with magnesium and hydrochloric acid developed a deep red colour. With concentrated sulphuric acid it exhibited no fluorescence.

3:7:2':5'-Tetrahydroxy flavone (VI a)

7-Hydroxy-3:2':5'-trimethoxy flavone (1 g.) was dissolved in acetic anhydride (20 c.c.) and to the solution was added hydriodic acid (10 c.c.; *d*, 1.7) cautiously with cooling. The solution was refluxed for 2 hours at 140°, diluted with sulphur dioxide water (100 c.c.) and left in the refrigerator overnight. The precipitated hydroxy-flavone was filtered off, washed thoroughly with sulphur dioxide water and finally with water. It was first crystallized from dilute alcohol and then from ethyl acetate-petroleum ether mixture when it came out as yellow tiny prisms melting at 270–71°; yield 0.4 g. (Found: C, 62.6; H, 3.9. $C_{15}H_{10}O_6$ requires C, 62.9; H, 3.6%). The tetrahydroxy flavone gave an olive-green colour with aqueous ferric chloride changing to red with excess of the reagent. With *p*-benzoquinone solution in alcohol it developed a dark red colour and it was soluble in aqueous bicarbonate and carbonate giving yellow solutions. With sodium hydroxide solution an orange-yellow colour was given and with concentrated sulphuric acid it exhibited no fluorescence.

5:7-Dihydroxy-3:2':5'-trimethoxy flavone (V b)

A mixture of ω -methoxy phloroacetophenone (2 g.), 2:5-dimethoxy benzoic anhydride (18 g.) and sodium gentisate (4 g.) was maintained at 180–85° for 4 hours under reduced pressure and the product worked up as usual. The flavonol was first crystallized from alcohol and finally from

ethyl acetate-petroleum ether mixture when it appeared as yellow soft needles melting at 271-72°; yield, 1.9 g. (Found: C, 62.9; H, 5.1. $C_{18}H_{16}O_7$ requires C, 62.8; H, 4.7%). It gave a red colour with magnesium and hydrochloric acid and a brownish red colour with aqueous ferric chloride and did not emit any fluorescence with concentrated sulphuric acid.

3:5:7:2':5'-pentamethoxy flavone (VIIc)

The above trimethyl ether (0.5 g.) was methylated using anhydrous acetone (75 c.c.), dimethyl sulphate (1.5 c.c.) and potassium carbonate (5 g.) and refluxing on a water-bath for a period of 40 hours. The pentamethoxy flavone crystallized from acetone as colourless aggregates of rectangular plates melting at 142-43°; yield, 0.47 g. (Found: C, 64.1; H, 5.5. $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4%). It did not give any colour with aqueous ferric chloride, was insoluble in cold dilute sodium hydroxide and developed a red colour on treatment with magnesium and hydrochloric acid. With concentrated sulphuric acid it gave no fluorescence.

3:5:7:2':5'-Pentahydroxy flavone (VIb)

The trimethoxy compound (Vb) (1 g.) was refluxed with acetic anhydride (20 c.c.) and hydriodic acid (10 c.c., d, 1.7) for 2 hours at 140° and the product worked up as usual. The flavone was first crystallized from dilute alcohol and finally from ethyl acetate-petroleum ether mixture when beautiful yellow tiny prisms were obtained decomposing at 306-8°; yield 0.45 g. (Found: C, 59.8; H, 3.6. $C_{15}H_{10}O_7$ requires C, 59.6; H, 3.3%). It gave an olive-green colour with aqueous ferric chloride changing to cherry red on the addition of excess of the reagent. With *p*-benzoquinone solution in alcohol it developed a deep red colour. It was soluble in aqueous sodium bicarbonate, carbonate and sodium hydroxide giving in each case a yellow solution and did not give any fluorescence with concentrated sulphuric acid.

2-Benzylxy-benzoic anhydride

2-Benzylxy benzoic acid required for this preparation was made according to the procedure adopted by Cohen and Dudley.⁶

To a suspension of the dry acid (22.8 g.) in anhydrous ether (100 c.c.) containing anhydrous pyridine (4 c.c.) was added thionyl chloride (3.6 c.c.) little by little with shaking at 0° over a period of 45 minutes. After the addition of thionyl chloride, the flask was left in the refrigerator overnight, the semisolid mass was taken up in ether and the ether extract was washed respectively with cold dilute hydrochloric acid, cold aqueous sodium bicarbonate and finally with cold water. It was then dried and the solvent distilled off when the anhydride was left as a dark viscous mass. Further

drying was done by leaving it in a vacuum over sulphuric acid for two days; yield 16 g. The crude product had a boiling range of 255–60°/10 mm. and was directly employed for the condensation as such without purification by distillation. It was most convenient to use it as a solution in dry chloroform and distil off the solvent before the condensation.

7-Hydroxy-3-methoxy-2'-benzyloxy flavone (VIII)

An intimate mixture of ω -methoxy resacetophenone (3 g.) 2-benzyloxybenzoic anhydride (20 g.) and sodium 2-benzyloxy benzoate (6 g.) was heated under reduced pressure at 180–85° for 4 hours. The product was worked up as in similar cases. The crude product was obtained as a viscous oil which did not solidify on keeping in the refrigerator for several days. It was then taken up in ether, dried over magnesium sulphate and the solvent distilled off. Now the viscous mass partially solidified on leaving it for about ten days in the refrigerator. The solid was collected and crystallized from a mixture of ether and acetone when it appeared as colourless aggregates of beautiful tiny plates and flat needles melting at 195–96°; yield 1.2 g. (Found: C, 74.0; H, 4.5. $C_{23}H_{18}O_5$ requires C, 73.8; H, 4.8%). The substance gave no colour with aqueous ferric chloride, was soluble in aqueous sodium carbonate and sodium hydroxide and with concentrated sulphuric acid it gave a lemon yellow solution without any fluorescence.

3: 7-Dimethoxy-2'-benzyloxy flavone (IX)

The above compound (VIII) (0.9 g.) was methylated in dry acetone (100 c.c.) by refluxing for 8 hours with anhydrous potassium carbonate (5 g.) and dimethyl sulphate (0.4 c.c.). The dimethoxy flavone crystallized from dry ether in the form of colourless rectangular prisms melting at 116–17°; yield, 0.8 g. (Found: C, 74.3; H, 5.3. $C_{24}H_{20}O_5$ requires C, 74.2; H, 5.2%). It was insoluble in aqueous sodium carbonate and sodium hydroxide and gave no colour with ferric chloride. With concentrated sulphuric acid it exhibited no fluorescence.

3: 7-Dimethoxy-2'-hydroxy flavone (X)

3: 7-Dimethoxy-2'-benzyloxy flavone (0.8 g.) was dissolved in glacial acetic acid (18 c.c.) and concentrated hydrochloric acid (12 c.c.) added. The contents were heated over a water-bath for ninety minutes, diluted with water (150 c.c.) and left in the refrigerator for 4 hours. The solid was collected, dried and crystallized from ethyl acetate when it appeared as colourless rectangular plates melting at 190–91°; yield, 0.35 g. (Found: C, 68.6; H, 4.8. $C_{17}H_{14}O_5$ requires C, 68.4; H, 4.7%). It was soluble in aqueous sodium carbonate and sodium hydroxide giving in each case lemon yellow solutions and exhibited no fluorescence in concentrated sulphuric acid solution.

3:7-Dimethoxy-2'-5'-dihydroxy flavone (XI)

To a stirred solution of the above flavone (X) (0.3 g.) in aqueous sodium hydroxide (0.35 g. in 10 c.c.) was added dropwise a saturated solution of potassium persulphate (0.8 g.) in the course of two hours, the temperature being kept between 15-20°. After 24 hours at room temperature the brown aqueous solution was neutralized with dilute hydrochloric acid to congo red, filtered and ether extracted. The aqueous layer was then acidified by the addition of further quantity of hydrochloric acid (10 c.c.) and the contents heated on a water-bath for 30 minutes when a brown solid slowly separated out. This was filtered, dried and crystallized from ethyl acetate when it came out as pale yellow rectangular rods and prisms melting at 237°; yield 0.08 g. (Found: C, 64.5; H, 4.7. $C_{17}H_{14}O_6$ requires C, 65.0; H, 4.5%). It developed no colour with alcoholic ferric chloride, was soluble in aqueous sodium carbonate and hydroxide giving lemon yellow solutions and with para-benzoquinone solution in alcohol it slowly developed a deep cherry red colour on keeping overnight. It did not exhibit fluorescence in concentrated sulphuric acid solution.

The dihydroxy compound (XI) was methylated using excess of dimethyl sulphate and anhydrous potassium carbonate in acetone medium. The tetramethoxy flavone (VII a) crystallized from a mixture of ethyl acetate and petroleum ether as colourless rectangular rods and flat needles melting at 169-70°. It did not give any colour with aqueous ferric chloride and was insoluble in aqueous alkali. The mixed melting point with the sample obtained from (V a) was not depressed.

SUMMARY

3:7:2'-5'-Tetrahydroxy flavone and 3:5:7:2':5'-pentahydroxy flavone and their derivatives are prepared and their colour reactions recorded. The flavone with only 2'-hydroxyl free (X) and also its 5'-hydroxyl derivative (XI) do not give any colour with ferric chloride indicating absence of chelation. Alkali colour reactions confirm the original finding that a quinol grouping in the side phenyl nucleus does not produce marked colour effects.

REFERENCES

1. Balakrishna, *et al.* .. *Proc. Ind. Acad. Sci.*, 1951, **33 A**, 151.
2. Baker .. *J.C.S.*, 1939, 961.
3. Rao and Seshadri .. *Proc. Ind. Acad. Sci.*, 1946, **24 A**, 375.
4. Rajagopalan, *et al.* .. *Ibid.*, 1947, **25**, 432.
5. Seshadri, *et al.* .. *Ibid.*, 1950, **32**, 251.
6. Mauthner .. *J. Prakt. Chem.*, 1915, **91**, 180.
7. Cohen and Dudley .. *J.C.S.*, 1910, **97**, 1745.