

SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part XLVII. A New Synthesis of 3-Hydroxy Primetin Derivatives

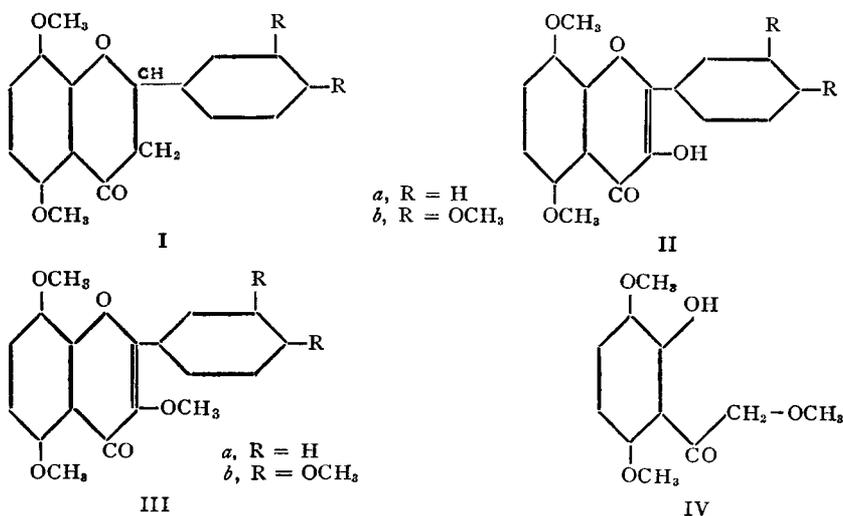
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THREE-Hydroxy primetin was prepared earlier by Seshadri *et al.*¹ by nuclear oxidation using 3-methoxy-5-hydroxy flavone. In view of the recent simplification in the preparation of 2-hydroxy-3:6-dimethoxy acetophenone,² the alternative method using this ketone as the starting point has now been adopted. Condensation with benzaldehyde to yield the corresponding chalcone has already been reported by Ballio and Pocchiari.³ The chalcone has now been converted into the corresponding flavanone (I *a*) and finally into the dimethoxy flavonol (II *a*) using a modification⁴ of the method of Kostanecki. The trimethoxy flavone (III *a*) obtained on methylation agrees with the sample prepared earlier.¹ As a useful reference compound for analytical study in this series, alkali fission of the trimethoxy flavone (III *a*) has been carried out and the properties of 2-hydroxy- ω :3:6-trimethoxy acetophenone (IV) recorded.

Using veratraldehyde in the above series of condensations 3:5:8:3':4' pentamethoxy flavone (III *b*) and the corresponding pentahydroxy flavone have also been prepared. The same pentamethyl ether is obtained by the



condensation of the fission ketone (IV) with the anhydride and sodium salt of veratric acid (Allan-Robinson condensation). That there is no isomeric change during the demethylation of the flavonol methyl ether (II *b*) by means of hydriodic acid has also been proved by the remethylation of the pentahydroxy flavone whereby the same pentamethoxy flavone (III *b*) is again formed. A similar report was made earlier in the preparation of 3-hydroxy primetin.¹

Recently Kurth and Hubbard⁵ isolated a pentahydroxy flavone from Ponderosa Pine Bark and concluded that it should have the constitution of 3:5:8:3':4'-pentahydroxy flavone. The properties recorded in this paper for the synthetic pentahydroxy flavone, its acetate and methyl ether do not agree with those of the natural product and its derivatives.

EXPERIMENTAL

5:8-Dimethoxy flavanone (I a)

2-Hydroxy-3:6-dimethoxy chalcone³ (1.5 g.) was refluxed with alcohol (100 c.c.) and conc. sulphuric acid (2.5 c.c.) for 35 hours, diluted with water (100 c.c.) and the alcohol distilled off under reduced pressure. The solid product crystallised from ethyl acetate as colourless prismatic needles and rods, m.p. 163–64° C. Yield, 1.0 g. (Found: C, 71.7; H, 5.6; C₁₇H₁₆O₄ requires C, 71.8; H, 5.6%). It gave no colour with alcoholic ferric chloride solution.

3-Hydroxy-5:8-dimethoxy flavone (II a)

The dimethoxy flavanone (0.5 g.) was dissolved in alcohol (50 c.c.) and to the boiling solution iso-amyl nitrite (3 c.c.) and conc. hydrochloric acid (30 c.c.) were added alternately in small quantities at a time, with stirring. The solution turned bright yellow first and finally bright reddish orange. The hot solution was allowed to cool slowly and stand for 2 hours with occasional shaking. It was then diluted with water (200 c.c.) and within a few minutes crystals of the flavonol separated out. This was filtered off and crystallised from ethyl alcohol as yellow needles and long rectangular plates, m.p. 191–92° C. Yield, 70 mg. (Found: C, 66.8; H, 4.5; C₁₇H₁₄O₅, $\frac{1}{2}$ H₂O requires C, 66.5; H, 4.9%). A further quantity (30 mg.) was obtained from the mother liquor which was extracted with ether. The ether solution was extracted with sodium hydroxide (2%) and the alkaline solution acidified and re-extracted with ether. On distilling off the solvent an oil was obtained. It was heated with a mixture of glacial acetic acid and concentrated hydrochloric acid (1:1; 10 c.c.) on a water-bath for 30 minutes. On dilution with water a solid product was obtained which on crystallisation from ethyl

alcohol melted at 191–92°. It gave a brown colour with alcoholic ferric chloride solution.

3:5:8-Trimethoxy flavone (III a)

3-Hydroxy-5:8-dimethoxy flavone (0.8 g.) was dissolved in acetone (150 c.c.) dimethyl sulphate (0.4 c.c., excess) and ignited potassium carbonate (2 g.) added and the mixture refluxed for 8 hours. The solution was filtered off, the solvent evaporated and the residue treated with water to decompose the excess of dimethyl sulphate. The solid product gave no colour with alcoholic ferric chloride solution and crystallised from methyl alcohol as pale yellow stout prisms melting at 169–70° alone or admixed with the sample prepared earlier.¹ Yield, 0.8 g. In the earlier description of the trimethoxy flavone the melting point was wrongly reported as 121–22°. On re-examination of the sample it was found to melt at 169–70°. The lower melting point seems to be therefore an error.

2-Hydroxy- ω :3:6-trimethoxy acetophenone (IV)

The above flavone (0.6 g.) was dissolved in absolute alcoholic potash (50 c.c.; 8%) and the solution refluxed over a water-bath for 8 hours. The alcohol was then distilled off and the residue treated with water (50 c.c.). The alkaline solution was extracted with ether to remove any unchanged product, acidified with hydrochloric acid and re-extracted with ether. The ether solution was washed with sodium bicarbonate and then with water. After the ether was distilled off, the residue crystallised from dry ether as deep yellow elongated and stout rectangular prisms, m.p. 102–3° C. Yield, 0.2 g. It gave a green colour with alcoholic ferric chloride solution (Found: C, 57.9; H, 5.9; C₁₁H₁₄O₅ requires C, 58.3; H, 6.2%).

3:5:8:3':4'-Pentamethoxy flavone (Allan-Robinson condensation) (III b)

An intimate mixture of the above ω -methoxy ketone (1 mol; 0.15 g.), veratric anhydride (2.5 mol; 0.58 g.), sodium veratrate (1.6 mol; 0.25 g.) was heated under reduced pressure at 170–80° for two and a half hours. The cooled product was dissolved in alcohol (36 c.c.) and water (3 c.c.) containing sodium hydroxide (3.7 g.), and the solution refluxed for 15 minutes. The alcohol was then removed under reduced pressure, and water (35 c.c.) added, when the pentamethoxy flavone separated out. It crystallised from ethyl alcohol as very pale yellow needles and rectangular prisms, and melted at 154–55° C.

5:8:3':4'-Tetramethoxy flavanone (I b)

2-Hydroxy-3:6:3':4'-tetramethoxy chalcone (1 g.) was dissolved in alcohol (100 c.c.) and concentrated sulphuric acid (2.5 c.c.) added. The

mixture was refluxed for 40 hours, and the product worked up as in the earlier case. The flavanone crystallised from a mixture of ethyl acetate and petroleum ether as colourless prismatic needles and rods; m.p. 141–42° (Found: C, 66.2; H, 5.6; $C_{19}H_{20}O_6$ requires C, 66.2; H, 5.8%).

3-Hydroxy-5:8:3':4'-tetramethoxy flavone (II b)

The tetramethoxy flavanone (0.5 g.), alcohol (40 c.c.), iso-amyl nitrite (3 c.c.) and concentrated hydrochloric acid (30 c.c.) were used according to the procedure already described. The main yield of the flavonol crystallised from methyl alcohol as yellow rectangular plates; m.p. 184–85°. Yield, 50 mg. (Found: C, 63.3; H, 5.2; $C_{19}H_{18}O_7$ requires C, 63.7; H, 5.0%). A further quantity (50 mg.) was obtained by working up the mother liquor as already described. The flavonol gave a brown colour with alcoholic ferric chloride.

The acetate was prepared by heating the above product with acetic anhydride and a drop of pyridine. It crystallised from ethyl acetate-petroleum ether mixture as almost colourless thick rhombohedral plates, m.p. 178–79°.

3:5:8:3':4'-Pentamethoxy flavone (III b)

The methylation of the above flavonol (50 mg.) was carried out using acetone (50 c.c.), dimethyl sulphate (0.43 c.c., excess) and potassium carbonate (1 g.) according to the procedure already given. The pentamethyl ether crystallised from a mixture of ethyl acetate and petroleum ether as very pale yellow needles and rectangular prisms; m.p. 154–55° C. Mixed melting point with the sample prepared by the Allan-Robinson method was undepressed. Yield, 40 mg. (Found: C, 64.4; H, 5.3; $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4%).

3:5:8:3':4'-Pentahydroxy flavone

5:8:3':4'-Tetramethoxy-3-hydroxy flavone (0.2 g.) was dissolved in acetic anhydride (5 c.c.) and to the cooled solution was added hydriodic acid (5 c.c.) carefully. The solution was refluxed for two hours in an oil-bath at 145–50°. It was then poured into crushed ice and treated with a saturated solution of sodium bisulphite (15 c.c.). The solid product was filtered and crystallised from dilute methyl alcohol when it separated as yellow tiny prisms; m.p. 265–66° with sintering at 248–50° C. Yield, 0.1 g. (Found: C, 59.3; H, 2.9; $C_{15}H_{10}O_7$ requires C, 59.6; H, 3.3%). With alcoholic ferric chloride it gave an olive green colour changing to olive brown; solutions in aqueous sodium hydroxide and carbonate had an orange colour which faded.

The *acetate* was prepared by heating the above product with acetic anhydride and a drop of dry pyridine. It crystallised from a mixture of methyl alcohol and ethyl acetate as lens-shaped crystals; m.p. 233–35° C.

The pentahydroxy flavone was remethylated in acetone solution with excess of dimethyl sulphate and potassium carbonate. The methyl ether crystallised from a mixture of ethyl acetate and petroleum ether, m.p. 154–55° C. Mixed melting point with pentamethoxy flavone obtained by the methylation of 5:8:3':4'-tetramethoxy flavonol and by the Allan-Robinson method was undepressed.

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SUMMARY

Starting from 2-hydroxy-3:6-dimethoxy acetophenone a new synthesis of 3-hydroxy primetin has been effected and by alkali fission of the trimethyl ether 2-hydroxy- ω :3:6-trimethoxy acetophenone has been prepared. Using the same procedure (modified Kostanecki's method) 3:5:8:3':4'-pentahydroxy flavone, its pentamethyl ether and penta-acetate have been obtained. The properties of these compounds are different from those of the pentahydroxy flavone and its derivatives obtained from Ponderosa Pine Bark.

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