5:6:7:8-HYDROXY-FLAVONOLS

Part IV. A Synthesis of Calycopterin

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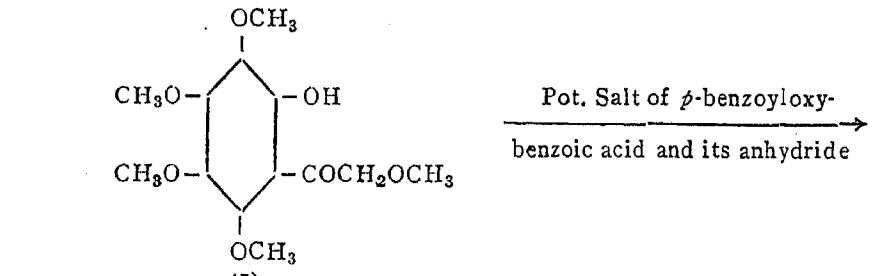
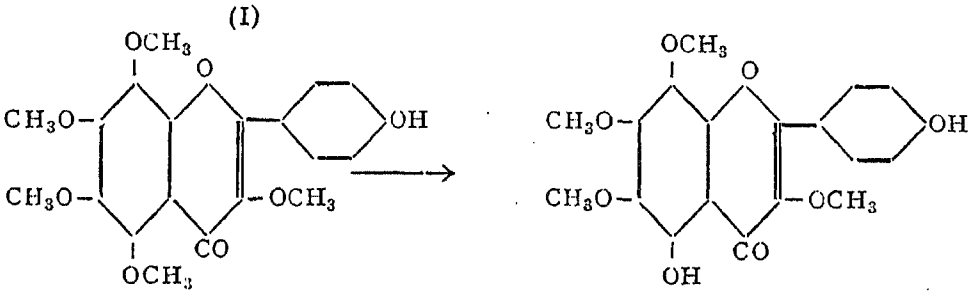
THE synthesis of calycopteretin and of its hexamethyl ether has already been reported.[1] The naturally occurring derivative, calycopterin is a partial methyl ether. Its constitution (III) has been established by a study of its degradation products and of its dimethyl and diethyl ethers[2, 3]. It has now been synthesised in the following manner. 2-Hydroxy-ω: 3:4:5:6-pentamethoxy-acetophenone (I) is condensed with the anhydride and potassium salt of *p*-benzoyloxy-benzoic acid according to the method of Allan and Robinson. The product is 4'-hydroxy-3:5:6:7:8-pentamethoxy-flavone (II) which when subjected to partial demethylation using hydrobomic acid[2] yields calycopterin (III).



(I)



(II) (III)

The synthetic and naturally occurring samples are identical in all their properties. The mixed melting point is undepressed. While preparing the acetyl derivative for purposes of comparison it is noticed that under milder conditions a mono-acetate could be made. Its properties indicate that it has the 5-hydroxyl free and that it is the 4'-acetate of calycopterin.

EXPERIMENTAL

p-Benzoyloxy-benzoic acid.—*p*-Hydroxy-benzoic acid (10·0 g.) was benzoylated using benzoyl chloride (10·0 c.c.) and sodium hydroxide

(100 c.c.; 10%) according to the Schotten-Baumann method. The solid product was filtered and crystallised from alcohol. It appeared as long colourless rectangular plates and prisms and melted at 220–22°.

The alkaline filtrate was acidified and the product obtained was filtered and washed with sodium carbonate solution. Thus some more benzoyloxy-benzoic acid could be obtained. (Found: C, 69·5; H, 4·3; $C_{14}H_{10}O_4$ requires C, 69·4; H, 4·1%.) The crystalline acid was sparingly soluble in cold dilute sodium hydroxide and sodium carbonate but went into solution on warming.

p-Benzoyloxy-benzoic anhydride.—Benzoyloxy-benzoic acid (10 g.) was treated with dry carbon tetrachloride (10 c.c.) and finely powdered phosphorus pentachloride (10·5 g.) and heated on a water-bath for 10 minutes until the evolution of hydrogen chloride ceased. The solvent and phosphorus oxychloride were then distilled off under reduced pressure and the solid product washed with a small volume of dry petroleum ether in the cold. When crystallised from carbon tetrachloride the acid chloride was obtained as colourless rectangular plates melting at 147–48°.

The acid chloride (10 g.) was dissolved in dry ether (200 c.c.), cooled in ice and pyridine (20 c.c.) added. The mixture was kept at ice temperature for two hours. At the end, the reaction mixture was treated with small bits of ice and the solid anhydride that separated filtered off. The ether solution was separated from the aqueous layer, washed successively with cold dilute hydrochloric acid, aqueous sodium carbonate and water, dried over anhydrous sodium sulphate and evaporated. The total anhydride (7 g.) was purified by crystallisation from dry benzene when it was obtained as colourless rectangular prisms melting at 155–57°. (Found: C, 72·5; H, 4·2; $C_{28}H_{18}O_7$ requires C, 72·1; H, 3·9%).

3 : 5 : 6 : 7 : 8-*Pentamethoxy-4'-hydroxy-flavone* (5-O-*Methyl-calycopterin*).—An intimate mixture of 2-hydroxy-ω: 3 : 4 : 5 : 6-pentamethoxy-acetophenone (0·75 g.), the above anhydride (8 g.) and the potassium salt of *p*-benzoyloxy-benzoic acid (3 g.) was heated at 175–80° for 3 hours. The product was then dissolved in alcohol (75 c.c.) and while boiling, a solution of potassium hydroxide (10 g. in 15 c.c.) added during half-an-hour and the boiling continued for another 20 minutes to decompose the anhydride. The alcohol was then removed under reduced pressure and the residue dissolved in water. It was filtered and the filtrate saturated with carbon dioxide. The precipitated flavone was dried and recrystallised several times from dry ethyl acetate when it appeared as pale yellow rectangular prisms melting at 200-202°. It was easily soluble in dilute

alkali to give a yellow solution and did not give any colour with alcoholic ferric chloride. Yield: 0·4 g. (Found: C, 61·7; H, 5·4; OCH_3, 39·9; $C_{20}H_{20}O_8$ requires C, 61·9; H, 5·2 and OCH_3, 40·0%).

5 : 4′-*Dihydroxy*-3 : 6 : 7 : 8-*tetramethoxy-flavone* (Calycopterin).—This was obtained by the demethylation of the above pentamethoxy-4′-hydroxy-flavone according to the method of Shah, Virkar and Venkataraman[2] using hydrobromic acid (50%) in acetic acid. The product was purified by crystallisation from ethyl acetate when it came out as bright yellow rectangular plates melting at 226–28°. It gave a green colour with alcoholic ferric chloride. A mixture of it with the natural sample of calycopterin showed no depression in melting point. (Found: C, 61·3; H, 4·8; OCH_3, 33·4; $C_{19}H_{18}O_8$ requires C, 61·0; H, 4·8 and OCH_3, 33·2%).

The *diacetate* was prepared by boiling with acetic anhydride and six drops of pyridine; it crystallised from alcohol as colourless long needles melting at 131–32°. The mixed melting point with the acetate of calycopterin from natural sources was undepressed.

Mono-acetate of Calycopterin.—When the synthetic or natural sample of calycopterin was boiled with acetic anhydride alone or with the addition of only a drop or two of pyridine, the monoacetate melting at 120–22° was produced. It was pale yellow in colour and crystallised from alcohol in the form of rectangular plates. It dissolved easily in dilute aqueous sodium hydroxide to form a yellow solution and gave a green colour with ferric chloride. These reactions indicated that the free hydroxyl was in the 5-position. (Found: C, 60·5; H, 5·2; $C_{21}H_{20}O_9$ requires C, 60·6 and H, 4·8%). It could be converted into the diacetate by further heating with acetic anhydride and 6-8 drops of pyridine.

Summary

By the condensation of 2-hydroxy-ω: 3 : 4 : 5 : 6-pentamethoxy-acetophenone with the anhydride and potassium salt of *p*-benzoyloxy-benzoic acid is obtained 4′-hydroxy-3 : 5 : 6 : 7 : 8-pentamethoxy-flavone which yields calycopterin by partial demethylation using hydrobromic acid.

References

1. Seshadri and Venkateswarlu .. *Proc. Ind. Acad. Sci.* (A), 1946, **23**, 192.
   Murti, Row and Seshadri .. *Ibid.*, 1946, **23**, 233.
2. Shah, Virkar and Venkataraman .. *J.I.C.S.*, 1942, **19**, 135.
3. Seshadri and Venkateswarlu .. *Proc. Ind. Acad. Sci.* (A) 1946, **23**, 209.