A Convenient Method for the Synthesis of Baicalein (5,6,7-Trihydroxyflavone) and 4'-Methylgamatin (4-Methoxy-3-methyl-7-phenylfuro-[3,2-*g*][1]benzopyran-5-one)

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We report a modified synthesis of baicalein by Dakin oxidation of 6-acetyl-5,7-dihydroxyflavone (I) (obtained by condensation of phloroacetophenone with ethyl benzoylacetate). and the elaboration of a furan ring on structure (I) by a conventional method to give 4'-methylgamatin.

SINCE the isolation of the angular furoflavone karanjin [1] from the seed oil of *Pongamia glabra* and recognition of its medicinal properties,[2] a number of furoflavones have been isolated from natural sources and their constitutions established by degradation and synthesis.[3] Amongst these, gamatin and pinnatin [3,4] have been

[1] G. D. Beal and M. C. T. Katti, *J. Amer. Pharm. Assoc.*, 1925, **14**, 1086; D. B. Limaye, *Abs. Proc. Indian. Sci. Congr.*, 1925, 118; 1926, 151.

[2] K. M. Nadakarni, Indian Materia Medica, p. 703. N. V. S. Rao, J. V. Rao, and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 1941, **13***A*, 414; 1943, **17***A*, 16.

[3] F. M. Dean, ' Naturally Occurring Oxygen Ring Compounds,' Butterworths, London, 1963, p. 312.

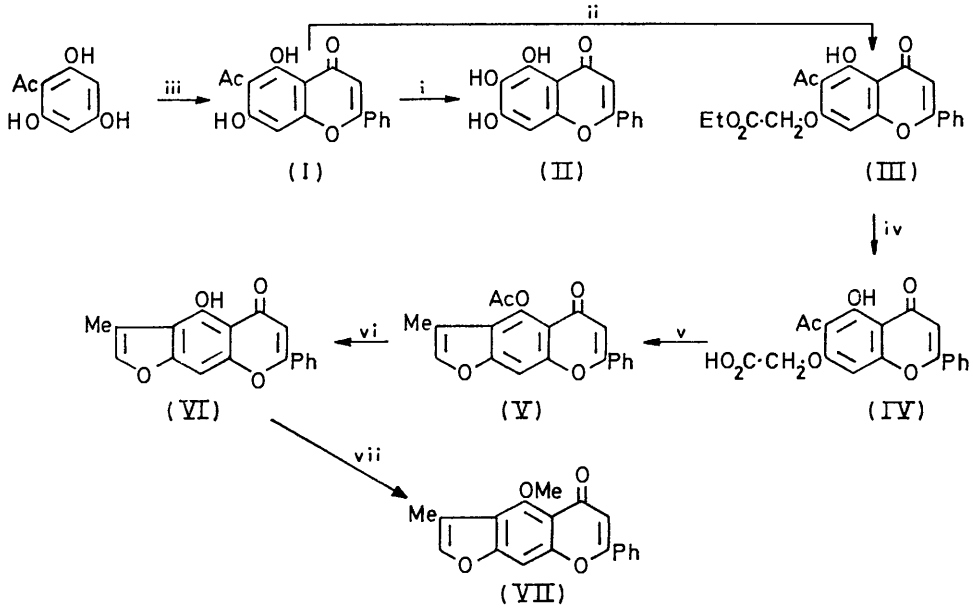
[4] L. R. Row, *Austral. J. Sci. Res.*, 1952, **6***A*, 754.

shown to have the furan ring fused in linear fashion. Whereas the synthesis of angular furo-compounds is relatively simple, suitable intermediates are not readily accessible for the synthesis of their linear isomers. We describe here a simple method for the preparation of such an intermediate, 5,7-dihydroxy-6-acetylflavone (I) and the synthesis of a linear furoflavone, 4'-methylgamatin (VII), from it. The intermediate (I) also served as an excellent precursor in the synthesis of baicalein (II), present in the roots of *Scutellaria baicalensis* and leaves of *S. Columnoe*.[5]

Reported methods for the synthesis of baicalein involve a number of steps and give a low overall yield.[6-8] The present method makes use of the easily accessible phloroacetophenone and ethyl benzoylacetate to give baicalein in only two steps and in high yield.

Treatment of phloroacetophenone with ethyl benzoylacetate in boiling diphenyl ether yielded 6-acetyl-5,7-dihydroxyflavone (I) in 62·5% yield; in this reaction the non-chelated hydroxy-group is involved in the formation of the γ-pyrone ring. Similar observations have been made in syntheses of 6-acetyl-5,7-dihydroxy-2-methylchromone [9] and 2-acetyl-1,3-dihydroxyxanthone [10] formation. The identity of compound (I) was established independently by its conversion into baicalein (5,6,7-trihydroxyflavone) (II) under the conditions of Dakin hydrogen peroxide oxidation. The product (II) was identified by its m.p.,[7] analytical data, colour reactions,[7,11] u.v. absorption [8] ($\lambda_{max.}$ 220, 275, and 323 nm, $\lambda_{min.}$ 240 and 300 nm), and conversion into the known trimethyl ether.[6,7]

The condensation of 6-acetyl-5,7-dihydroxyflavone (I) with ethyl bromoacetate in presence of anhydrous potassium carbonate in acetone yielded only 6-acetyl-7-ethoxycarbonylmethoxy-5-hydroxyflavone (III), since the hydroxy-group in position 5 is strongly chelated by both the pyrone carbonyl and the acetyl group. Further saponification of this, either with aqueous sodium carbonate (5%) in acetone or with 1 : 1 aqueous hydrochloric acid gave 6-acetyl-7-carboxymethoxy-5-hydroxyflavone (IV). This, when treated with freshly fused sodium acetate and acetic anhydride, not only underwent cyclisation with simultaneous decarboxylation but also suffered 5-*O*-acetylation yielding 4-acetoxy-3-methyl-7-phenylfuro[3,2-*g*][1]benzopyran-5-one (V).



Reagents: i, alkaline H_2O_2; ii, $BrCH_2{\cdot}CO_2Et$, and anh. K_2CO_3; iii, $BzCH_2{\cdot}CO_2Et$–Ph_2O; iv, hydrolysis; v, Ac_2O–AcONa; vi, saponification; vii, methylation

Saponification of (V) with hydrochloric acid gave the 4-hydroxy-compound (VI), which was readily methylated to give 4'-methylgamatin (VII).

EXPERIMENTAL

6-Acetyl-5,7-dihydroxyflavone (I).—A mixture of phloroacetophenone (5 g) and ethyl benzoylacetate (10 ml) in diphenyl ether (25 ml) was heated under reflux for 1·5 h. After cooling, ether was added and the solid was collected and washed with ether. Crystallisation from acetic acid gave the *flavone* (I) as pale yellow needles (5·5 g), m.p. 240° (Found: C, 68·5; H, 4·3. $C_{17}H_{12}O_5$ requires C, 68·9; H, 4·05%). An ethanolic solution gave a dark red colouration with aqueous iron(III) chloride.

Baicalein (5,6,7-*Trihydroxyflavone*) (II).—To an ice cold solution of 6-acetyl-5,7-dihydroxyflavone (1 g) in aqueous 4% sodium hydroxide (10 ml), 30% hydrogen peroxide

[5] Ref. 3, p. 297.
[6] V. D. N. Shastri and T. R. Seshadri, *Proc. Indian Acad. Sci.* 1946, **23***A*, 262.
[7] A. Schonberg, N. Badran, and N. A. Starkowsky, *J. Amer. Chem. Soc.*, 1955, **77**, 5390.
[8] M. Jouanne and C. Mentzer, *Compt. rend.*, 1962, **254**, 727.
[9] M. M. Badawi and M. B. E. Fayez, *Tetrahedron*, 1965, **21**, 2925.
[10] Y. S. Agasimundin and S. Rajagopal, *J. Org. Chem.*, 1971, **36**, 845.
[11] A. Mustafa, N. A. Starkovsky, and E. Zaki, *J. Org. Chem.*, 1960, **25**, 794.

(3·5 ml) was added. The mixture was left overnight in the refrigerator. It was then acidified; the precipitate crystallised from aqueous acetic acid to give baicalein as yellow prisms (0·6 g), m.p. 263—264° (lit.,[8] 262°; lit.,[6,7] 263—264°), $\lambda_{max.}$ 220, 275, and 323 nm, $\lambda_{min.}$ 240 and 300 nm [8] (Found: C, 66·45; H, 3·4. Calc. for $C_{15}H_{10}O_5$: C, 66·65; H, 3·7%). The product dissolved in aqueous 4% sodium hydroxide developing a green colour, and gave a greenish brown colour with iron(III) chloride.[7] It also gave a red-brown colour with aqueous 1% uranyl acetate solution, which changed to brown on dilution with water.[11]

Methylation in dry acetone with methyl iodide and anhydrous potassium carbonate gave the trimethyl ether which crystallised from ethanol as needles, m.p. 167—168° (lit.,[6] 165—166°; lit.,[7] 165—167°).

6-*Acetyl-7-ethoxycarbonylmethoxy-5-hydroxyflavone* (III).—A solution of 6-acetyl-5,7-dihydroxyflavone (1·8 g) in dry acetone (200 ml), containing anhydrous potassium carbonate (10 g), was treated with ethyl bromoacetate (1 ml) under reflux for 15 h. The product that separated as a salt was filtered off, suspended in water, and acidified. The solid that separated was crystallised from ethanol to give the *ester* (III) as needles (1·8 g), m.p. 154—155° (Found: C, 65·65; H, 4·6. $C_{21}H_{18}O_7$ requires C, 65·95; H, 4·7%), which gave a dark red colour with aqueous iron(III) chloride.

Acetyl-7-carboxymethoxy-5-hydroxyflavone (IV).—(*a*) To a solution of compound (III) (1·4 g) in acetone (250 ml), aqueous sodium carbonate (5%; 60 ml) was added and the mixture was heated under reflux for 3 h. Acetone was distilled off and the aqueous solution, on acidification gave the acid (IV). Crystallisation from ethanol yielded thin *plates* (1 g), m.p. 242—243° (Found: C, 64·65; H, 3·7. $C_{19}H_{14}O_7$ requires C, 64·4; H, 4·05%). An ethanolic solution gave a dark red colouration with aqueous iron(III) chloride.

(*b*) A mixture of the ester (III) (1·8 g) and 1 : 1 aqueous hydrochloric acid (36 ml) was heated under reflux for 1 h, then cooled. Crystallisation of the deposited solid from ethanol gave 6-carboxymethoxy-5-hydroxyflavone as thin plates (1·4 g), m.p. 242—243°.

4-*Acetoxy-3-methyl-7-phenylfuro*[3,2-g][1]*benzopyran-5-one* (V).—A mixture of the acid (IV) (0·7 g) and freshly fused sodium acetate (1 g) in acetic anhydride (10 ml) was heated under reflux for 2 h. The product was poured into ice–water and the solid that separated after some time was filtered off and washed with aqueous sodium hydrogen carbonate and water. Crystallisation from ethanol gave the *furoflavone* as pale yellow rectangular plates (0·6 g), m.p. 222° (Found: C, 71·95; H, 4·1. $C_{20}H_{14}O_5$ requires C, 71·85; H, 4·2%), giving no colour with iron(III) chloride.

4-*Hydroxy-3-methyl-7-phenylfuro*[3,2-g][1]*benzopyran-5-one* (VI).—The furoflavone (V) (0·5 g) was hydrolysed by refluxing in 1 : 1 aqueous hydrochloric acid (10 ml) for 1 h. The product, which separated on cooling, was filtered off and crystallised from ethanol to give the *hydroxyfuroflavone* as tiny yellow needles (0·35 g), m.p. 211—212° (Found: C, 73·1; H, 4·3. $C_{18}H_{12}O_4$ requires C, 73·0; H, 4·05%), giving a green colouration with aqueous iron(III) chloride.

4′-*Methylgamatin* (4-*Methoxy-3-methyl-7-phenylfuro*-[3,2-g][1]*benzopyran-5-one*) (VII).—To a solution of compound (VI) (0·3 g) in dry acetone (100 ml), methyl iodide (2 ml) and anhydrous potassium carbonate (4 g) were added. The mixture was refluxed for 8 h, inorganic salts were filtered off, and the solution was evaporated. The residue crystallised from ethanol to give 4′-*methylgamatin* as rectangular plates (0·25 g), m.p. 190° (Found: C, 74·1; H, 4·25. $C_{19}H_{14}O_4$ requires C, 74·5; H, 4·55%), which gave no colour with aqueous iron(III) chloride.

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