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A SYNTHESIS OF 6:8-DIHYDROXYFLAVONE

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Abstract—Work on routes to the synthesis of 6:8-dihydroxyflavone, one of which proved successful, is described.

6:8-DIHYDROXYFLAVONE which, until recently, was the only unknown of the six possible dihydroxyflavones unsubstituted in the 2-phenyl group, has proved unexpectedly difficult to synthesise.[1] We have explored a number of routes and have now obtained 6:8-dimethoxyflavone in 4 per cent yield by a Mentzer reaction[2] involving the thermal condensation of 2:4-dimethoxyphenol with ethyl benzoylacetate.[3] Simpson[4] synthesised 6:8-dihydroxyflavone shortly before the above work was completed and courteously agreed to simultaneous publication of preliminary notes.[3,4] Demethylation of the dimethoxyflavone required prolonged treatment with hydriodic acid. Thermal condensation of resorcinol with ethyl 3-oxo-2-phenylpropionate gave 7-hydroxy-3-phenylcoumarin and not 7-hydroxy*iso*flavone.[5]

8-Amino-6-methoxyflavone was also synthesised but it was not found possible to replace the amino by the hydroxyl group. 6-Methoxyflavone was readily produced by treatment of 6-methoxy-5-*p*-tolylsulphonyloxyflavone with hydrogen in presence of Raney nickel,[6] but the method failed with 6:8-dimethoxy-5-*p*-tolylsulphonyloxyflavone. Other unsuccessful approaches are mentioned in the experimental section.

Rajagopalan, Seshadri, and Varadarajan's synthesis[7] of 5:6:8-trihydroxyflavone includes the interaction of 5-hydroxy-8-methoxyflavone with hexamine to give 6-formyl-5-hydroxy-8-methoxyflavone. We obtained mainly di-(5-hydroxy-8-methoxyflavon-6-yl)methane from this reaction, and found it preferable to hydroxylate (Elbs persulphate method) 5-hydroxy-6-methoxyflavone in the 8-position.

EXPERIMENTAL

Crystallisation was from ethanol unless otherwise stated.

6:8-*Dihydroxyflavone*

2:4-Dimethoxyphenol[8] (10 g) was heated under an air condenser at 270° for 8 hr with ethyl benzoylacetate[9] (15 g). A current of nitrogen was used to remove ethanol and water as formed. The residue was extracted with ether and the ethereal solution

[1] W. Baker, N. C. Brown and J. A. Scott *J. Chem. Soc.* 1922 (1939).
[2] C. Mentzer, D. Molho and P. Vercier *C.R. Acad. Sci., Paris* **232**, 1488 (1951); D. Pilion, *Bull. Soc. Chim. Fr.* 39 (1955).
[3] J. E. Gowan, S. P. MacGiolla Riogh, G. J. MacMahon, B. R. O'Farrell, S. Ó'Cléirigh, E. M. Philbin and T. S. Wheeler *Chem. and Ind. (Rev.)* 1672 (1955).
[4] T. H. Simpson *Chem. and Ind. (Rev.)* 1672 (1955).
[5] W. Baker *J. Chem. Soc.* 2898 (1927).
[6] G. W. Kenner and M. A. Murray *J. Chem. Soc.* S178 (1949).
[7] S. Rajagopalan, T. R. Seshadri and S. Varadarajan *Proc. Indian Acad. Sci.* A31, 31 (1950).
[8] E. Späth, M. Pailer and G. Gergely *Chemie.* **73**, 935 (1940).
[9] R. L. Shriner, A. G. Schmidt and L. J. Roll *Org. Synth. Coll.* **2**, 266 (1943).

was washed with dilute alkali (solution A—see below) and with water. Removal of the solvent gave an oil which was chromatographed on alumina. The chromatogram was developed with light petroleum (b.p. 40–60°). Five bands were observed in ultra-violet light. The first four were eluted with light petroleum and the fifth, which proved to be 6:8-*dimethoxyflavone*, with benzene-petroleum ether (30 : 70). This compound separated from ligroin in needles (0·5 g), m.p. 148–149° and 152–153° (dimorphic) (Found: C, 72·6; H, 5·0; OMe, 22·4. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0; 2OMe, 22·0 per cent). Dr. T. H. Simpson (personal communication) states that the m.p. was not depressed by addition of 6:8-dimethoxyflavone synthesised by him from the corresponding chalkone.[4]

Demethylation by hydriodic acid–acetic anhydride under reflux for 4 hr gave 6:8-*dihydroxyflavone*, which crystallised from aqueous ethanol in yellow needles, m.p. 274° (decomp.) (Found: C, 71·2; H, 4·1. $C_{15}H_{10}O_4$ requires C, 70·9; H, 4·0 per cent). 6:8-*Diacetoxyflavone* formed needles, m.p. 196–197° (Found: C, 67·0; H, 4·2. $C_{19}H_{14}O_6$ requires C, 67·4; H, 4·2 per cent). Each of the three flavones in sulphuric acid solution exhibited a yellow fluorescence in ultra-violet light.

Acidification of the alkaline solution A (above) gave 3-benzoyl-3:4-dihydro-2:4-di-oxo-6-phenyl-2*H*-pyran, m.p. and mixed m.p. with an authentic sample prepared by refluxing ethyl benzoylacetate,[10] 170–172°.

Wavelengths for maximum light absorption in ethanolic solution (λ_{max} in mμ) are shown below for some 6- and 8-substituted flavones: 6-hydroxyflavone (271,303); 8-hydroxyflavone (267); 6:8-dihydroxyflavone (276); 6-methoxyflavone (267,302); 8-methoxyflavone (265); 6:8-dimethoxyflavone (275); 6-acetoxyflavone (255,296); 8-acetoxyflavone (254,295); 6:8-diacetoxyflavone (257,297).

7-Hydroxy-3-phenylcoumarin

Resorcinol (15 g) was heated with ethyl 3-oxo-2-phenylpropionate (15 g) in nitrogen at 270–280° until evolution of water and ethanol ceased (15 min). The product was refluxed with acetone (1·5 l), dimethyl sulphate (20 g), and potassium carbonate (200 g) for 6 hr, solids were removed, and the filtrate diluted with water (2 l). The ethereal solution of the resulting precipitate was washed with alkali. The residue after removal of the solvent was chromatographed on alumina. The fourth band which was visible in ultra-violet light, was eluted by light petroleum and yielded 7-methoxy-3-phenylcoumarin, which crystallised in prisms (0·7 g), m.p. 124° (Found: C, 76·5; H, 4·7; OMe, 12·2. Calc. for $C_{16}H_{12}O_3$: C, 76·2; H, 4·8; OMe, 12·3 per cent). Demethylation by hydriodic acid in acetic anhydride gave 7-hydroxy-3-phenylcoumarin which separated from aqueous ethanol in prisms, m.p. 207°. Baker[5] gives m.p. 124° for the methoxycoumarin and m.p. 207–208° for the hydroxycoumarin.

Numerous unsuccessful attempts[11] were made to apply Ruhemann's flavone synthesis[12] to the preparation of 6:8-dihydroxyflavone. This synthesis involves cyclisation of 3-aryloxycinnamoyl halides prepared from the adducts of phenols to 3-arylpropiolic esters.

Methyl 2-hydroxy-3:5-dimethoxybenzoate

A mixture of 2:3:5-trimethoxybenzoic acid,[1] acetic anhydride, and hydriodic acid

[10] A. Baeyer and W. H. Perkin *Chemie.* **17**, 64 (1884).
[11] B. R. O'Farrell M.Sc. Thesis, National University of Ireland (1956).
[12] S. Ruhemann *Chemie.* **46**, 2188 (1913); **54**, 912 (1921).

was heated at 60° for 12 hr, and the product was added to aqueous sodium hydrogen sulphite. The precipitated *2-hydroxy-3:5-dimethoxybenzoic acid* separated from water in needles, m.p. 183° (Found: C, 54·4; H, 4·9; OMe, 31·5. $C_9H_{10}O_5$ requires C, 54·5; H, 5·1; 2OMe, 31·3 per cent), which gave a blue colour with ethanolic ferric chloride. The *methyl ester* (Fischer-Speier) crystallised from water in needles, m.p. 92° (Found: C, 56·4; H, 5·7; OMe, 43·3. $C_{10}H_{12}O_5$ requires C, 56·6; H, 5·7; 3OMe, 43·8 per cent), which exhibited a green ethanolic ferric colour. The positive ethanolic ferric reactions of the acid and ester confirmed that, as expected, demethylation had occurred *ortho* to the carbonyl group. No useful result was obtained in attempts to prepare benzoyl-2-hydroxy-3:5-dimethoxybenzoylmethane (the hydroxydiketone corresponding to 6:8-dimethoxyflavone) by a Claisen condensation of this ester with acetophenone using sodium in dry xylene.

8-Amino-6-methoxyflavone

A mixture of 2-hydroxy-5-methoxyacetophenone[1] (10 g), acetic acid (120 ml), and acetic anhydride (9 ml) was cooled to solidification and treated with nitric acid (3·0 ml; *d* 1·5); after 1 hr the liquid-solid product was added to ice.

2-Hydroxy-5-methoxy-3-nitroacetophenone, which separated, crystallised from methanol in yellow plates (7·2 g), m.p. 112° (Found: C, 50·9; H, 4·2: N, 6·7. $C_9H_9O_5N$ requires C, 51·2; H, 4·3; N, 6·6 per cent). This ketone was oriented by hypobromite oxidation.[13] The product did not depress the m.p. of an authentic sample of 2-hydroxy-5-methoxy-3-nitrobenzoic acid.[14]

No useful result was obtained in attempts to nitrate 2:5-diacetoxyacetophenone or 2:5-dimethoxyacetophenone. The *2:4-dinitrophenylhydrazone* of this latter ketone formed red needles, m.p. 170° (Found: C, 53·7; H, 4·5; N, 16·1; OMe, 17·1. $C_{16}H_{16}O_6N_4$ requires C, 53·3; H, 4·5; N, 15·6; 2OMe, 17·2 per cent).

Methylation of 2-hydroxy-5-methoxy-3-nitroacetophenone (methyl sulphate-potassium carbonate-acetone) gave *2:5-dimethoxy-3-nitroacetophenone* which crystallised in plates, m.p. 52–53° (Found: C, 53·6; H, 4·9; N, 5·9; OMe, 28·2. $C_{10}H_{11}O_5N$ requires C, 53·3; H, 4·9; N, 6·2; 2OMe, 27·6 per cent).

2-Benzoyloxy-5-methoxy-3-nitroacetophenone which was prepared by the action of pyridine and benzoyl chloride on 2-hydroxy-5-methoxy-3-nitroacetophenone formed plates, m.p. 105–106° (Found: C, 61·0; H, 4·2; N, 4·6; OMe, 9·8. $C_{16}H_{13}O_6N$ requires C, 61·0; H, 4·2; N, 4·4; OMe, 9·8 per cent). A mixture of this ester (15 g), potassium hydroxide (3 g), and pyridine (60 ml) was shaken for 72 hr and the product was added to ice and hydrochloric acid. The precipitate of *benzoyl-2-hydroxy-5-methoxy-3-nitrobenzoylmethane* crystallised in red needles (4·5 g), m.p. 124° (Found: C, 60·6; H, 4·3; N, 4·6; OMe, 9·9. Required: as for the ester). The ethanolic ferric colour was red.

A solution of the diketone in acetic acid containing a trace of hydrochloric acid was boiled for 45 min, and then diluted with water. *6-Methoxy-8-nitroflavone* which separated, formed needles, m.p. 196–197° from acetic acid (Found: C, 64·3; H, 4·0; N, 4·8; OMe, 9·7. $C_{16}H_{11}O_5N$ requires C, 64·6; H, 3·7; N, 4·7; OMe, 10·4 per cent). Reduction by stannous chloride in hydrochloric acid yielded *8-amino-6-methoxyflavone* which crystallised in yellow needles, m.p. 204–205° (Found: C, 71·9; H, 5·1;

[13] W. S. Johnson, C. D. Gutsche and R. D. Offenhauer *J. Amer. Chem. Soc.* **68**, 1648 (1946).
[14] A. Klemenc *Mh. Chem.* **33**, 1243 (1912).

N, 5·2; OMe, 12·3. $C_{16}H_{13}O_3N$ requires C, 71·9; H, 4·9; N, 5·2; OMe, 11·6 per cent). *8-Acetamido-6-methoxyflavone* separated from methanol in needles, m.p. 254–256° (Found: C, 70·0; H, 5·1; N, 4·5; OMe, 10·2. $C_{18}H_{15}O_4N$ requires C, 69·9; H, 4·9; N, 4·5; OMe, 10·0 per cent). The aminoflavone when refluxed with picryl chloride in ethanol for 15 min gave *6-methoxy-8-picrylaminoflavone* which formed orange needles, m.p. 236–238° (Found: C, 55·2; H, 3·1; N, 11·6; OMe, 6·8. $C_{22}H_{14}O_4N_4$ requires C, 55·2; H, 3·0; N, 11·7; OMe, 6·5 per cent).

Many unsuccessful attempts were made by diazotisation and subsequent hydrolysis to convert 8-amino-6-methoxyflavone into 8-hydroxy-6-methoxyflavone.[15,16] Other experiments involved efforts at direct replacement of the amino group by hydroxyl by treatment with acid.[16,17] An endeavour was also made to convert 8-acetamido-6-methoxyflavone into the 8-hydroxy compound by the action of alkali.[18] 6-Methoxy-8-picrylaminoflavone was also resistant to acid and alkaline hydrolysis. No success was obtained in essays to apply a Bucherer-type reaction to the aminoflavone.

Di-(5-hydroxy-8-methoxyflavon-6-yl)methane

A mixture of 5-hydroxy-8-methoxyflavone (0·6 g),[7] acetic acid (20 ml), and hexamine (2·0 g) was heated at 100° for 6 hr, and hydrochloric acid (20 ml; 1 : 1) was added. Heating was continued for 1 hr and the product was diluted with water. The precipitated *diflavonylmethane* separated from benzene in yellow needles (0·15 g), m.p. 299–300° (Found: C, 72·6; H, 4·6. $C_{33}H_{24}O_8$ requires C, 73·3; H, 4·4 per cent). The ethanolic ferric colour was green. The *di-acetate* formed microcrystals from nitrobenzene, m.p. 318–322° (Found: C, 70·1; H, 4·7. $C_{37}H_{28}O_{10}$ requires C, 70·3; H, 4·5 per cent).

5:6:8-*Trihydroxyflavone*

Aqueous potassium persulphate (1·7 g in 50 ml water) was added at 15–20° during 2 hr to a stirred suspension of 5-hydroxy-6-methoxyflavone[19] (1 g) in water (20 ml) containing potassium hydroxide (1.2 g) and pyridine (30 ml). After 48 hr the solution was acidified to congo red and unchanged hydroxymethoxyflavone removed. The filtrate was heated with sodium sulphite (3 g) and hydrochloric acid (30 ml) at 100° for 1 hr. It then yielded to ether crude 5:8-dihydroxy-6-methoxyflavone which was crystallised from methanol. The crystals (0·07 g) when refluxed with hydroidic acid and acetic acid for 2 hr gave 5:6:8-trihydroxyflavone, m.p. 237–239° (acetate, m.p. 217–218°). Rajagopalan, Seshadri, and Varadarajan[7] give m.p. 236–237° and 214°. Acetylation of the crude 5:8-dihydroxy-6-methoxyflavone yielded *5:8-diacetoxy-6-methoxyflavone* which crystallised from methanol in needles, m.p. 199–201° (Found: C, 64·9; H, 4·3. $C_{20}H_{16}O_7$ requires C, 65·2; H, 4·4 per cent). This acetate when treated with ethanolic hydrochloric acid at 100° for 30 min gave *5:8-dihydroxy-6-methoxyflavone* which crystallised from aqueous ethanol in reddish needles, m.p. 254° (decomp.) (Found: C, 68·0; H, 4·5; OMe, 10·8. $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·3; OMe, 10·9 per cent). A mixture of the dihydroxymethoxyflavone (0·2 g)

[15] N. Anand and K. Venkataraman *Proc. Indian Acad. Sci.* **A26**, 279 (1947); Bräunlich "Beilstein" **6**, 769 (1923); Ad. Claus and R. Wallbaum *J. Prakt. Chem.* **56**, 48 (1897); A. Hantzsch and E. Jochem *Chemie.* **34**, 3337 (1901); H. H. Hodgson and J. Walker *J. Chem. Soc.* 1620 (1933); Woodward *Org. Synth.* **25**, 55 (1945).

[16] R. N. Iyer and K. Venkataraman *Proc. Indian Acad. Sci.* **A37**, 629 (1953).

[17] C. Graebe *Chemie.* **16**, 862 (1883); E. Späth and E. Dobrovolny *Ibid.* **71**, 1831 (1938).

[18] W. W. Hartman, J. R. Byers and J. B. Dickey *Org. Synth. Coll.* **2**, 451 (1943).

[19] W. Baker *J. Chem. Soc.* 956 (1939).

ethanol (40 ml), water (16 ml), potassium carbonate (2 g) and dimethyl sulphate (1 ml) was shaken for 30 min[20] and the product was diluted with water. The precipitate of *5-hydroxy-6:8-dimethoxyflavone* separated from methanol in light brown needles (0·12 g), m.p. 183–184° (Found: C, 68·2; H, 5·1; OMe, 20·7. $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7; 2OMe, 20·8 per cent).

5-Hydroxy-6-methoxyflavone on treatment with *p*-toluenesulphonyl chloride, acetone, and potassium carbonate yielded *6-methoxy-5-p-tolylsulphonyloxyflavone*, m.p. 204–206° (from acetone) (Found: C, 65·4; H, 4·4; S, 7·5. $C_{23}H_{18}O_6S$ requires C, 65·4; H, 4·3; S, 7·6 per cent). Reduction of the sulphonyloxyflavone by the hydrogen-Raney nickel method[6] gave 6-methoxyflavone (mixed m.p. confirmation). *6:8-Dimethoxy-5-p-tolylsulphonyloxyflavone* crystallised from acetic acid in aggregates, m.p. 246–247° (Found: C, 64·1; H, 4·7; S, 7·5. $C_{24}H_{20}O_7S$ requires C, 63·7; H, 4·5; S, 7·1 per cent). Attempts to obtain 6:8-dimethoxyflavone by hydrogenolysis of the above compound in the presence of Raney nickel were unsuccessful.

α- and β-4-Hydroxyflavan

Hydrogen was passed during 2 hr through an ethanolic solution (500 ml) of 5-*p*-tolylsulphonyloxyflavone (1 g) containing Raney nickel (6 g). Solids were removed and the filtrate was concentrated to 20 ml. The precipitate formed on addition of water gave a trace of α-4-hydroxyflavan (soluble in hot water) which formed needles, m.p. 119–120° (Found: C, 79·8; H, 6·4. Calc. for $C_{15}H_{14}O_2$: C, 79·6; H, 6·2 per cent) (acetate, m.p. 84–85°). Freudenberg and Orthner[21] give m.p. 119° and 85–86°. The water-insoluble fraction (β-4-hydroxyflavan) separated from ligroin in needles, m.p. 143–144° (Found: C, 79·1; H, 6·4. Calc. as above) (acetate, m.p. 98°). Karrer, Yen, and Reichstein[22] give m.p. 148–149° and 97–98°. Gupta, Jain, and Seshadri[23] obtained only the β-compound from 5- and 7-*p*-tolylsulphonyloxyflavone.

No satisfactory result was obtained in attempts to remove the sulphonyloxy group from 6-methoxy-5-*p*-tolylsulphonyloxyflavone by Clar's method (zinc dust, sodium chloride, zinc chloride)[24] or by the use of lithium aluminium hydride.[25]

Diethyl flavon-7-yl phosphate

A mixture of tetra-ethylpyrophosphate (6 ml), 7-hydroxyflavone (2·5 g), and N-sodium hydroxide (10 ml) was shaken for 2 hr, diluted with water, and extracted with ether. The ethereal solution was washed successively with dilute alkali, acid, and water. Removal of the solvent gave *diethyl flavon-7-yl phosphate* which formed plates, m.p. 60–61° (0·7 g) from light petroleum (b.p. 40–60°) (Found: C, 60·6; H, 5·2; P, 8·1. $C_{19}H_{19}O_6P$ requires C, 61·0; H, 5·1; P, 8·3 per cent). This compound was not altered by treatment with sodium in liquid ammonia.[26]

7-Chloroflavone

7-Hydroxyflavone (1 g) was heated with phosphorus oxychloride (4 g) until

[20] J. M. Guider, T. H. Simpson and D. B. Thomas *J. Chem. Soc.* 170 (1955).
[21] K. Freudenberg and L. Orthner *Chemie.* **55**, 1748 (1922).
[22] P. Karrer, Y. Yen and I. Reichstein *Helv. Chim. Acta* **13**, 1308 (1930).
[23] V. N. Gupta, A. C. Jain and T. R. Seshadri *Proc. Indian Acad. Sci.* **A38**, 470 (1953); R. Mozingo and H. Adkins *J. Amer. Chem. Soc.* **60**, 669 (1938).
[24] E. Clar *Chemie.* **72**, 1645 (1939); H. W. D. Stubbs and S. H. Tucker *J. Chem. Soc.* 2939 (1951).
[25] P. Karrer and H. Schmid + *Helv. Chim. Acta* **32**, 1371 (1949); C. W. Shoppee and D. D. Evans *J. Chem. Soc.* 540 (1953).
[26] G. W. Kenner and N. R. Williams *J. Chem. Soc.* 522 (1955).

hydrogen chloride was no longer evolved (3 hr), and the product was extracted with hot water. The residual 7-chloroflavone separated from methanol (charcoal) in aggregates (0·8 g), m.p. 155–157° (Found: C, 70·6; H, 3·5: Cl, 14·2. Calc. for $C_{15}H_9O_2Cl$: C, 70·2; H, 3·5; Cl, 13·8 per cent). Cramer and Elschnig[27] give m.p. 158°. *7-Chloroflavone hydrazone* crystallised from aqueous ethanol in needles, m.p. 178–180°. (Found: C, 65·8; H, 4·0; N, 10·4. $C_{15}H_{11}ON_2Cl$ requires C, 66·5; H, 4·1; N, 10·2 per cent.)

7-Bromoflavone

7-Hydroxyflavone (5 g) was fused with phosphorus pentabromide (13 g) and sodium chloride (1 g) for 1 hr, and the product was extracted with hot water. The residue separated from methanol in micro-crystals (0·4 g), m.p. 157–158° (Found: C, 59·8; H, 3·2. Calc. for $C_{15}H_9O_2Br$: C, 59·8; H, 3·0 per cent). Chen and Chang[28] give m.p. 162–163° for 7-bromoflavone.

Experiments on the replacement of halogen by hydrogen in 7-halogenoflavones were discontinued on the synthesis of 6:8-dimethoxyflavone. These experiments involved the conversion of the halogenoflavone, through the lithium derivative, into the corresponding carboxylic acid.

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[27] F. Cramer and G. H. Elschnig *Chemie.* **89**, 10 (1956).
[28] F. C. Chen and K. T. Chang, *J. Taiwan Pharm. Assoc.* **4**, 38 (1952); *Chem. Abstr.* **49**, 3175 (1955).