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SHORT COMMUNICATION

THE SYNTHESIS OF 3-METHYLFISETIN AND SOME METHYL ETHERS OF KAEMPFEROL

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Abstract—The naturally occurring flavones, 3′,4′,7-trihydroxy-3-methoxyflavone (3-methylfisetin), 4′,5-dihydroxy-3,7-dimethoxyflavone (kumatakenin), 4′,5,7-trihydroxy-3-methoxyflavone (kaempferol 3-methyl ether) and 3,5-dihydroxy-4′,7-dimethoxyflavone, have been synthesized by the Allan–Robinson method.

3-*O*-Methylfisetin,* a new naturally occurring flavone isolated from black wattle (*Acacia mearnsii*) heartwood extract, was assigned the structure (Ib) on the basis of spectroscopic and degradation studies.[1] Of the large number of flavonoid compounds[2–4] isolated from the extracts of black wattle, only the flavonol glycoside mearnsitrin,[5] containing a methoxyl group in the 4′-position, and 3-*O*-methylfisetin are methoxylated. The isolation of the latter compound has been considered interesting[1] in the light of speculation concerning the biosynthesis of C_{16} flavonoids either by condensation of C_{15} flavonoids with formaldehyde,[6] or by photochemical oxidative cyclization.[7] We now report a synthesis of (Ib) which confirms the proposed structure. Condensation of 2,4-dihydroxy-ω-methoxyacetophenone with 3,4-dibenzyloxybenzoic anhydride in the presence of triethylamine by the Allan–Robinson method yielded a hydroxyflavone (Ia) which on debenzylation with concentrated hydrochloric acid in glacial acetic acid furnished the desired flavone (Ib). Although the melting point of the synthetic compound (Ib) is higher than that reported for 3-methylfisetin, comparison of their i.r. spectra and TLC behaviour showed that the two specimens were identical.

Kimura and his co-workers recently isolated a dihydroxydimethoxyflavone named kumatakenin from the seeds of *Alpinia kumatake*[8] and *A. japonica*.[9] From their chemical studies they concluded that it was a new flavone and assigned it as 4′,5-dihydroxy-3,7-dimethoxyflavone (IIc). This led us to synthesize flavone (IIc). Condensation of 2,4,6-trihydroxy-ω-methoxyacetophenone with *p*-benzyloxybenzoic anhydride in the presence of triethylamine yielded 4′-benzyloxy-5,7-dihydroxy-3-methoxyflavone (IIa), which on monomethylation with dimethyl sulphate afforded 4′-benzyloxy-5-hydroxy-3,7-dimethoxyflavone

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* This substance is named incorrectly as 3-methoxyfisetin in the original report.[1]

[1] S. E. Drewes and A. H. Ilsley, *Chem. Commun.* 1246 (1968).

[2] H. H. Keppler, *J. Chem. Soc.* 2721 (1957).

[3] S. E. Drewes and D. G. Roux, *Biochem. J.* **87**, 167 (1963) and references cited therein.

[4] D. G. Roux and E. Paulus, *Biochem. J.* **82**, 320 (1962).

[5] A. M. Mackenzie, *Tetrahedron Letters* **26**, 2519 (1967).

[6] W. R. Chan, W. G. C. Forsyth and C. H. Hassall, *J. Chem. Soc.* 3174 (1958); S. E. Drewes and D. G. Roux, *J. Chem. Soc.* (c) 1644 (1966).

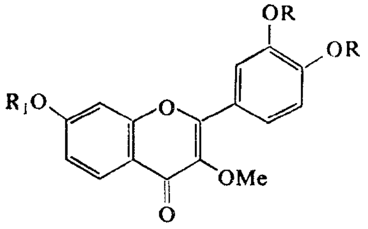
[7] A. C. Waiss and J. Corse, *J. Am. Chem. Soc.* **87**, 2068 (1965); A. C. Waiss, R. E. Lundin, A. Lee and J. Corse, *J. Am. Chem. Soc.* **89**, 6213 (1967).

[8] Y. Kimura, M. Takido, S. Takahashi and M. Kimishima, *Yakugaku Zasshi* **87**, 440 (1967); *Chem. Abs.* **67**, 9394 (1967).

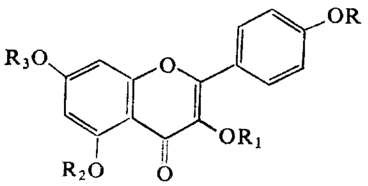
[9] Y. Kimura, M. Takido and S. Takahashi, *Yakugaku Zasshi* **87**, 1132 (1967); *Chem. Abs.* **68**, 968 (1968).

(IIb). Debenzylation of (IIb) with concentrated hydrochloric acid in glacial acetic acid yielded the desired flavone (IIc). After the completion of the synthesis we became aware that Jefferies and Payne[10] had earlier isolated a dihydroxydimethoxyflavone from a new *Beyeria* species and established its structure as 4′,5-dihydroxy-3,7-dimethoxyflavone (IIc) from degradative and spectroscopic studies. A comparison of our synthetic compound with the natural product from the *Beyeria* species showed that they were identical but, unfortunately, no sample of kumatakenin was available for comparison. Two syntheses of flavone (IIc) have recently been reported.[11, 12] Although one of the methods described[11] is similar to that of ours, no experimental details were given and the reported melting point of the intermediate (IIb) is different from that obtained by us.

4′,5,7-Trihydroxy-3-methoxyflavone (IIf) is the aglycone of the unusual glycoside isolated from the leaves of *Begonia manicata*.[13] Its assigned structure was confirmed by its identity with the product obtained from the controlled monomethylation of kaempferol.[13]



(Ia) $R=C_6H_5CH_2, R_1=H$
(Ib) $R=R_1=H$
(Ic) $R=R_1=CH_3CO$
(Id) $R=R_1=C_6H_5CO$



(IIa) $R=C_6H_5CH_2, R_1=Me, R_2=R_3=H$
(IIb) $R=C_6H_5CH_2, R_1=R_3=Me, R_2=H$
(IIc) $R=R_2=H, R_1=R_3=Me$
(IId) $R=R_2=CH_3CO; R_1=R_3=Me$
(IIe) $R=R_2=Et, R_1=R_3=Me$
(IIf) $R=R_2=R_3=H, R_1=Me$
(IIg) $R=R_2=R_3=CH_3CO, R_1=Me$
(IIh) $R=R_2=R_3=C_6H_5CO, R_1=Me$
(IIi) $R=R_2=R_3=Et, R_1=Me$
(IIj) $R=R_3=Me, R_1=R_2=H$
(IIk) $R=R_3=Me, R_1=R_2=CH_3CO$
(IIl) $R=R_3=Me, R_1=R_2=Et$

This flavone (IIf), synthesized earlier by Seshadri and his co-workers,[14] has also recently been isolated from various *Centaurea* species by Bohlmann and Zdero.[15] We now provide another synthesis of this flavone by the debenzylation of (IIa), an intermediate obtained in the above synthesis of kumatakenin (IIc). The melting point of the synthetic flavone (IIf) obtained is higher than that reported[13, 14] but its TLC behaviour and its i.r. spectrum were identical to those of an authentic specimen.[13]

3,5-Dihydroxy-4′,7-dimethoxyflavone (IIj) was recently isolated from the leaves of the fern *Cheilanthes farinosa*,[16] and its structure was established by analytical and spectroscopic

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[10] P. R. Jefferies and T. G. Payne, *Australian J. Chem.* **18**, 1441 (1965).

[11] C. P. Bahl, M. R. Parthasarthy and T. R. Seshadri, *Current Sci.* (*India*) **35**, 281 (1966).

[12] L. Farkas, A. Gottsegen and M. Nogradi, *Acta Chim.* (*Budapest*) **55**, 311 (1968); *Chem. Abs.* **69**, 4846 (1968).

[13] J. B. Harborne and E. Hall, *Phytochem.* **3**, 453 (1964).

[14] K. V. Rao and T. R. Seshadri, *J. Chem. Soc.* 122 (1947).

[15] F. Bohlmann and C. Zdero, *Tetrahedron Letters* **33**, 3239 (1967).

[16] H. Erdtman, L. Novotny and M. Romanuk, *Tetrahedron* **22**, Suppl. 8, Part 1, p. 71 (1966).

studies. This flavone (IIj), previously synthesized[17] by the bismuth acetate oxidation of 3,5-dihydroxy-4′-7-dimethoxyflavanone, has also been obtained from the hydrolysis of the product formed by the controlled methylation of kaempferol 3-L-rhamnoside, which was isolated from the bark of *Engelhardtia formosana.*[18] In the course of our work on other flavones[19] we required flavone (IIj) and we have synthesized it by the Allan–Robinson reaction 2,6-dihydroxy-4-methoxy-ω-benzoyloxyacetophenone with anisic anhydride and sodium anisate. The synthetic compound (IIj) was found to be identical to the natural product isolated from *Ch. farinosa.*

EXPERIMENTAL

M.ps. were determined in a Hoover capillary apparatus. I.r. spectra were determined in Nujol using Perkin–Elmer 137 and 337 instruments. TLC was carried out with Merck silica gel G and either $CHCl_3$ or $CHCl_3$–acetone (4:1).

3′,4′-Dibenzyloxy-7-Hydroxy-3-Methoxyflavone (Ia)

A mixture of 2,4-dihydroxy-ω-methoxyacetophenone[20] (0·55 g), 3,4-dibenzyloxybenzoic anhydride (4·9 g), and NEt_3 (1·6 ml) was heated in an oil-bath at 150–160° for 3 hr. The NEt_3 was removed under reduced pressure and the residue refluxed with 10% alcoholic KOH (15 ml) for 20 min. The solvent was removed under reduced pressure and water (120 ml) was added to dissolve the residue. Saturation of the solution with CO_2 yielded a gel which was extracted with ether. The ether extract was washed successively with aqu. $NaHCO_3$, Na_2CO_3 and water. Evaporation of the dried ether extract afforded a residue which crystallized from acetone–methanol as creamish needles (Ia) (0·44 g), m.p. 171–172° (Found: C, 74·68; H, 5·14. $C_{30}H_{24}O_6$ required: C, 74·99; H, 5·03 per cent). Acidification of the Na_2CO_3 extract yielded a mixture of 2,4-dibenzyloxybenzoic acid and the dibenzyl ether (Ia), as detected by TLC, from which a further amount (0·16 g) of the latter was isolated.

3′,4′,7-Trihydroxy-3-Methoxyflavone (3-Methylfisetin) (Ib)

A solution of the dibenzyl flavone (Ia) (0·23 g) in glacial HOAc (5 ml) and conc. HCl (5 ml) was heated on a water-bath for 45 min. Water (50 ml) was added to the mixture and the resulting pale-yellow solution was neutralized with solid $NaHCO_3$ and then saturated with NaCl. The precipitate was collected and crystallized from aqueous ethanol in pale-yellow needles (Ib), m.p. 282–284° (Found: C, 63·83; H, 4·24. $C_{16}H_{12}O_6$ required: C, 64·00; H, 4·03 per cent). (Although the reported[1] m.p. of 3-methylfisetin is 268–270°, the compound provided by Dr. Drewes melted at 276–279° and the mixed m.p. with synthetic (Ib) was 276–280°. The two specimens also showed identical TLC behaviour and i.r. spectrum.) The flavone (Ib) gave an intense green colour with $FeCl_3$ in alcohol. It was sparingly soluble in $CHCl_3$, ether and ethyl acetate but readily soluble in acetone and alcohols. It readily dissolved in aqu. Na_2CO_3 forming a deep-yellow solution.

The flavone (Ib) was further characterized by the preparation of a triacetate by the acetic anhydride–pyridine method. It crystallized from methanol in colourless prisms (Ic), m.p. 146–147° (lit., 145–147°) (Found: C, 61·92; H, 4·74. $C_{22}H_{18}O_9$ required: C, 61·97; H, 4·26 per cent). Prepared similarly, the tribenzoate (Id) separated from acetone in colourless needles, m.p. 169–171° (Found: C, 71·96; H, 4·24. $C_{37}H_{24}O_9$ required: C, 72·54; H, 3·95 per cent).

4′-Benzyloxy-5,7-Dihydroxy-3-Methoxyflavone (IIa)

A mixture of 2,4,6-trihydroxy-ω-methoxyacetophenone[21] (5·0 g), *p*-benzyloxybenzoic anhydride (36·3 g), and NEt_3 (13·8 ml) was heated on an oil-bath at 140–150° for 3 hr. The amine was removed under reduced pressure and the red residue was dissolved in ethanol (50 ml) and the solution refluxed with 10% alcoholic KOH (80 ml) for 20 min. The solvent was removed under reduced pressure and addition of water (140 ml) yielded the insoluble potassium *p*-benzyloxybenzoate which was filtered off. The basic filtrate was saturated with CO_2 and the resulting precipitate, consisting of a mixture of flavone (IIa) and potassium *p*-benzyloxybenzoate, was collected. The mixture was treated with dil. HCl and the product was collected and triturated with acetone–methanol to remove the more soluble *p*-benzyloxybenzoic acid. The insoluble flavone (IIa)

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[17] J. M. Guider, T. H. Simpson and (in part) D. B. Thomas, *J. Chem. Soc.* 170 (1955).

[18] T. Tominaga, *J. Pharm. Soc. Japan* **75**, 1399 (1955); *Chem. Abs.* **50**, 9396 (1956).

[19] K. Y. Sim, *J. Chem. Soc.* (c) 976 (1967).

[20] W. K. Slater and H. Stephen, *J. Chem. Soc.* **117**, 309 (1920).

[21] R. Robinson and K. Venkataraman, *J. Chem. Soc.* **135**, 61 (1929).

(4·2 g) was collected and sublimed at 225–235°/0·15 mm to give yellow leaflets, m.p. 284–286° (Found: C, 70·82; H, 4·86. $C_{23}H_{18}O_6$ required: C, 70·80; H, 4·61 per cent). This flavone (IIa) is very sparingly soluble in common organic solvents. Fractional sublimation *in vacuo*, which removes the *p*-benzyloxybenzoic acid at 170–175°/0·15 mm, is also a convenient way of isolating the flavone from the mixture.

4′-*Benzyloxy*-5-*Hydroxy*-3,7-*Dimethoxyflavone* (*IIb*)

Methylation of flavone (IIa) (98 mg) with dimethyl sulphate (58 mg) and anhydrous K_2CO_3 (2 g) in boiling acetone (30 ml) for 4 hr afforded the methyl ether (IIb) which was purified by chromatography on silica gel and then recrystallized from acetone–methanol in pale-yellow needles (43 mg), m.p. 142–144° (Seshadri and co-workers reported[11] m.p. 131–132°) (Found: C, 71·49; H, 5·17. $C_{24}H_{20}O_6$ required: C, 71·28; H, 4·99 per cent), giving an intense olive-green coloration with $FeCl_3$ in alcohol.

4′,5-*Dihydroxy*-3,7-*Dimethoxyflavone* (*IIc*)

Conc. HCl (4 ml) was added to a solution of flavone (IIb) (150 mg) in HOAc (4 ml) and the mixture was heated on a water-bath for 1 hr. Water (50 ml) was added and the precipitate was collected and recrystallized from acetone in yellow needles (85 mg), m.p. 252–254° (Found: C, 64·62; H, 4·77. Calc. for $C_{17}H_{14}O_6$: C, 64·96; H, 4·49 per cent), undepressed on admixture with sample of natural 4′,5-dihydroxy-3,7-dimethoxyflavone[10] and having the same i.r. spectrum and TLC behaviour (lit.,[8,10] m.p. 246–247° and 253–254°). The flavone was further characterized by the preparation of its diacetate (IId), m.p. 165–167° (lit.,[8,10] m.p. 165–167°) (Found: C, 63·42; H, 4·80. Calc. for $C_{21}H_{18}O_8$: C, 63·31; H, 4·55 per cent).

4′,5-*Diethoxy*-3,7-*Dimethoxyflavone* (*IIe*)

Ethylation of flavone (IIc) (62 mg) with diethyl sulphate (110 mg) and anhydrous K_2CO_3 (3 g) in boiling acetone for 48 hr furnished the diethyl ether (IIe) which recrystallized from methanol in colourless needles, m.p. 142–144° (Found: C, 67·97; H, 6·21. $C_{21}H_{22}O_6$ required: C, 68·09; H, 5·99 per cent).

4′,5,7-*Trihydroxy*-3-*Methoxyflavone* (*Kaempferol* 3-*Methyl Ether*) (*IIf*)

A solution of flavone (IIa) (0·5 g) in HOAc (110 ml) and conc. HCl (80 ml) was heated on a water-bath for 1 hr. Water (600 ml) was added and the precipitate (0·3 g) was collected and recrystallized from aqueous ethanol in yellow needles (IIf), m.p. 299–302° (Found: C, 64·21; H, 4·44. Calc. for $C_{16}H_{12}O_6$: C, 64·00; H, 4·03 per cent), having the same i.r. spectrum and TLC behaviour as an authentic sample of 3-O-methylkaempferol[13] (lit.,[13,15] m.p. 272–276° and 270–272°). Unfortunately, there was insufficient of the authentic sample for a mixed m.p. determination. The flavone was further characterized by the preparation of the triacetate (IIg), m.p. 163–165° (lit.,[15] 161–163°) (Found: C, 62·22; H, 4·61. Calc. for $C_{22}H_{18}O_9$: C, 61·97; H, 4·26 per cent); the tribenzoate (IIh), m.p. 157–160° (Found: C, 72·37; H, 4·06. $C_{37}H_{24}O_9$ required: C, 72·54; H, 3·95 per cent); and the triethyl ether (IIi), m.p. 144–146° (Found: C, 69·00; H, 6·36. $C_{22}H_{24}O_6$ required: C, 68·73; H, 6·29 per cent).

3,5-*Dihydroxy*-4′,7-*Dimethoxyflavone* (*IIj*)

A mixture of 2,6-dihydroxy-4-methoxy-ω-benzoyloxyacetophenone[22] (1·5 g), anisic anhydride (8·0 g), and sodium anisate (1·5 g) was heated in an oil-bath at 165–175° for 3 hr. The resulting black residue was dissolved in ethanol (35 ml) and the solution refluxed with 8 % alcoholic KOH (70 ml) for 20 min. The solvent was removed under reduced pressure and water (100 ml) was added to the residue. The solution was saturated with CO_2 and the precipitate was collected and recrystallized from acetone–methanol as yellow needles (IIj) (0·8 g), m.p. 178–180° (Found: C, 65·01; H, 4·56. Calc. for $C_{17}H_{14}O_6$: C, 64·96; H, 4·49 per cent) (lit.,[16–18] m.p. 179–180° and 180–182°), undepressed on admixture with the natural product[16] and the two specimens showed identical TLC behaviour and i.r. spectrum. The flavone (IIj) was also characterized by the preparation of the diacetate (IIk), m.p. 193–195° (lit.,[18] m.p. 194–195°); and a diethyl ether (IIl), m.p. 157–158° (Found: C, 68·33; H, 6·20. $C_{21}H_{22}O_6$ required: C, 68·09; H, 5·99 per cent).

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[22] R. KUHN and I. LOW, *Berichte* 77, 202 (1944).