614. *The Chemistry of Extractives from Hardwoods. Part VIII.* The Isolation of* 5 : 4′-*Dihydroxy*-7-*methoxy*iso*flavone* (*Prunetin*) *from the Heartwood of* Pterocarpus angolensis *and a Synthesis of* 7 : 4′-*Dihydroxy*-5-*methoxy*iso*flavone hitherto known as Prunusetin.*

By F. E. King and L. Jurd.

A further extractible constituent of *Pterocarpus angolensis* (see *J.*, 1952, 96, 1920) is shown to be 5 : 4′-dihydroxy-7-methoxy*iso*flavone (prunetin).

By starting from genistein, the isomeric 7 : 4′-dihydroxy-5-methoxy*iso*flavone has been synthesised for the first time. It is not identical with the natural product prunusetin (Chakravarti and Bhar, *J. Indian Chem. Soc.*, 1945, **22**, 301) which on the evidence now available cannot be distinguished from prunetin.

Alcoholic extracts of the commercial timber muninga (*Pterocarpus angolensis*), from which 6 : 4′-dihydroxy-5 : 7-dimethoxy*iso*flavone (muningin) and 2 : 4-dihydroxyphenyl 1-*p*-methoxyphenylethyl ketone (angolensin) have recently been obtained, also contain 5 : 4′-dihydroxy-7-methoxy*iso*flavone (prunetin) (I; R = H). On prolonged methylation

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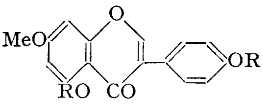
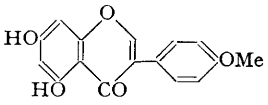
* Part VII, *J.*, 1952, 1920.

the new product formed a dimethyl ether shown by direct comparison with an authentic specimen to be 5 : 7 : 4′-trimethylgenistein (I; R = Me). Thereafter, its identity with genistein 7-methyl ether (I; R = H), first isolated by Finnemore (*Pharm. J.*, 1910, **31**, 604) from the bark of a *Prunus* species, was evident from the correspondence in melting points of their respective mono- and di-acetates, monomethyl ethers, and monomethyl ether acetates. Prunetin diethyl ether has a higher melting point than that recorded for a compound of that description recently synthesised (Narasimhachari and Seshadri, *Proc. Indian Acad. Sci.*, 1950, **32**, 256).

Of the three possible monomethyl ethers of genistein, the structures of two, namely, prunetin (I; R = H) and biochanin-A (5 : 7-dihydroxy-4′-methoxy*iso*flavone) (II), extracted by Sidiqui from germinated Chana grain (*J. Sci. Ind. Res., India*, 1945, **4**, 68; Bose and Siddiqui, *ibid.*, p. 231) have been firmly established by syntheses (Iyer, Shah, and Venkataraman, *Current Sci.*, 1949, **18**, 404; Shriner and Hull, *J. Org. Chem.*, 1945, **10**, 288, respectively). The remaining *O*-monomethylgenistein (III; R = H) has not so far been obtained synthetically but is reported to occur in the bark of *Prunus puddum* (Chakravarti and Bhar, *J. Indian Chem. Soc.*, 1945, **22**, 301) and has been called prunusetin. The reported melting points of prunusetin (237—238°) and of its diacetate (220—222°), which is the sole characteristic derivative prepared by Chakravarti and Bhar, do not appreciably differ from those recorded by Finnemore (*loc. cit.*) for prunetin (242° corr.) and prunetin diacetate (224—226°); consequently, there was at first some doubt as to the precise orientation of the dihydroxymethoxy*iso*flavone derived from *Pterocarpus angolensis* (m. p. 237—238°; diacetate, 222—225°). However, the intense ferric colour reaction exhibited by the muninga extractive, a characteristic property of the chelated 5-hydroxyl group, appeared decisively to exclude the structure (III; R = H) and, the properties of (II) being obviously different, it was thus possible to identify the heartwood constituent as prunetin (I; R = H).

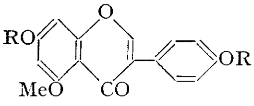
(I)

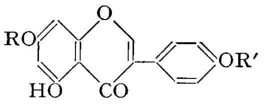




(II)

(III)





(IV)

Chakravarti and Bhar record for their dihydroxymethoxy*iso*flavone a similar well-marked ferric reaction, but nevertheless regard it as (III; R = H) largely from its formation of a dimethyl ether (I; R = Me), in apparent contrast to prunetin from which Finnemore (*loc. cit.*) obtained only a monomethyl derivative. The Indian authors were apparently unaware that the methylation conditions they employed do not correspond with those recorded by Finnemore, and, when we applied the two different procedures to the dihydroxymethoxy*iso*flavone from muninga, prunetin monomethyl ether (5-hydroxy-7 : 4′-dimethoxy*iso*flavone) (IV; R = R′ = Me) was obtained on methylation with methyl iodide and sodium methoxide in methanol (Finnemore's method), whereas the reagent used by Chakravarti and Bhar (methyl iodide, potassium carbonate) afforded the dimethyl ether (I; R = Me). The principal evidence differentiating the supposed 7 : 4′-dihydroxy-5-methoxy*iso*flavone of Chakravarti and Bhar from its isomer prunetin is thereby invalidated. Its identification as the 5-methyl ether of genistein (III; R = H) was further discredited by the completion of a synthesis of this compound which has shown that the new *iso*flavone has m. p. 302° (diacetate, m. p. 169·5°) and exhibits only a very feeble ferric reaction. The so-called prunusetin of Chakravarti and Bhar on the evidence now available is indistinguishable from prunetin (I; R = H).

Genistein was the starting point for our synthesis of the new *iso*flavone (III; R = H). Considerable quantities were available in the form of its 4′-methyl ether, biochanin-A (II), which had been obtained during large-scale extractions of the heartwood of *Ferreirea* *spectabilis* (F. E. King, M. F. Grundon, and K. G. Neill, forthcoming publication). Genistein, obtained by the demethylation of (II), under prolonged treatment with benzyl chloride and sodium carbonate or sodium ethoxide gave a dibenzyl ether, chelation of the 5-hydroxyl group limiting the reaction to the formation of 7 : 4′-dibenzyloxy-5-hydroxy-*iso*flavone (IV; R = R′ = CH_2Ph). Further alkylation with methyl iodide and potassium carbonate afforded the corresponding methyl ether (III; R = CH_2Ph) from which the required 5-methylgenistein (III; R = H) was obtained by debenzylation in a solution of hydrochloric and acetic acids.

The availability of biochanin-A was utilised in a synthesis of 7-hydroxy-5 : 4′-dimethoxy*iso*flavone formerly obtained by hydrolysis of trimethylgenistin (genistein-7-D-glucoside trimethyl ether) and by partial demethylation of 5 : 7 : 4′-trimethylgenistein (Walz, *Annalen*, 1931, **489**, 118). The *iso*flavone (II) was monobenzylated and the 7-benzyl ether then methylated, the resulting 7-benzyloxy-5 : 4′-dimethoxy*iso*flavone being hydrolysed under mild conditions to a product identical with that obtained by Walz.

EXPERIMENTAL

Isolation of Prunetin (I; R = H).—After removal of muningin from an alcoholic extract of the powdered wood by crystallisation from methanol as already described (*J.*, 1952, 98), the dark resinous solid (750 g.) obtained on evaporating the solvent was finely powdered and heated under reflux with acetone (2·5 l.) for 1 hour. Insoluble material was then removed by filtration and the filtrate concentrated to approx. 1 l. and diluted with ether (4 l.). When the dark red granular precipitate containing a further small amount of muningin had been collected, the dark acetone–ether solution was twice washed with N-sodium hydroxide (total 1 l.). The use of this limited quantity of alkali enabled the prunetin to be retained by the mixture of organic solvents which was then washed with water, dried ($MgSO_4$), and evaporated. The yellow oily residue was dissolved in an equal weight of hot methanol, the *iso*flavone separating overnight as a pale yellow solid (6·2 g.), m. p. 236°. Recrystallisation from methanol gave pale cream-coloured silky needles m. p. 237—238° (Found: C, 67·3; H, 4·5; OMe, 9·8. Calc. for $C_{16}H_{12}O_5$: C, 67·6; H, 4·3; OMe, 10·9%). In alcoholic solution it gave a deep brown-purple colour with ferric chloride. With acetic anhydride and sodium acetate on a steam-bath for 45 minutes diacetylprunetin was formed, and it crystallised from methanol in flat thick rods, m. p. 222·5° (Found: C, 65·0; H, 4·4; OMe, 8·7. Calc. for $C_{20}H_{16}O_7$: C, 65·2; H, 4·4; 1OMe, 8·4%).

A solution of prunetin (0·1 g.) in pyridine (0·4 c.c.) briefly warmed with acetic anhydride (0·25 c.c.) and poured into water gave 4′-acetoxy-5-hydroxy-7-methoxy*iso*flavone, which when successively crystallised from benzene–light petroleum and methanol formed fine needles, m. p. 187° (Finnemore, *loc. cit.*, records 190°) (Found: C, 66·2; H, 4·5; OMe, 7·9. Calc. for $C_{18}H_{14}O_6$: C, 66·2; H, 4·3; 1OMe, 9·5%). In alcoholic solution the ferric reaction was intense red-violet.

Prunetin Dimethyl Ether (I; R = Me).—The action of methyl iodide (5 c.c.) and potassium carbonate (3 g.) on prunetin (1 g.) in refluxing acetone for 24 hours gave 5 : 7 : 4′-trimethoxy*iso*flavone which crystallised from benzene–light petroleum in thin plates (0·98 g.), m. p. 161·5° alone or mixed with a specimen prepared from biochanin-A. From the oxidation of prunetin dimethyl ether with nitric acid on a steam-bath, 4-methoxy-3-nitrobenzoic acid was isolated on the addition of water. Recrystallisation gave needles, m. p. and mixed m. p. 192—193°.

Unlike prunetin, the dimethyl ether dissolved in hot concentrated hydrochloric acid and deposited, on cooling, yellow needles of the readily hydrolysed *iso*flavone hydrochloride.

Hydrolysis of the dimethyl ether (0·2 g.) with potassium hydroxide (1 g.) in water (2 c.c.) and alcohol (20 c.c.) under reflux for 2 hours afforded 2-hydroxy-4 : 6-dimethoxyphenyl 4-methoxybenzyl ketone, which after evaporation of the alcohol and acidification was isolated by ether-extraction. Crystallised from light petroleum it had m. p. 87° (lit., 88—89°) (Found: C, 67·7; H, 6·1. Calc. for $C_{17}H_{18}O_5$: C, 67·5; H, 6·0%).

5-*Hydroxy*-7 : 4′-*dimethoxy*iso*flavone* (*Prunetin Monomethyl Ether*) (IV; R = R′ = Me).—(i) A mixture of prunetin (0·25 g.), methyl sulphate (0·12 g., 1·1 mols.), anhydrous potassium carbonate (1 g.), and acetone (25 c.c.) was heated under reflux for 5 hours. The product, precipitated after filtration and on the addition of water, crystallised from methanol, whereupon prunetin monomethyl ether was obtained in flat needles (0·18 g.), m. p. 144° (Found: C, 68·8; H, 5·2; OMe, 19·6. Calc. for $C_{17}H_{14}O_5$: C, 68·4; H, 4·7; 2OMe, 20·8%). With alcoholic ferric chloride the ether gave an intense red colour.

(ii) When excess of ethereal diazomethane was added to a suspension of prunetin (50 mg.) in methanol a clear solution was obtained from which prunetin monomethyl ether began to separate. Isolated by evaporation of the solvents and crystallised from methanol it had m. p. 138—139°.

(iii) Repetition of the procedure described by Finnemore (*loc. cit.*), using methyl iodide in methanolic sodium methoxide, though less satisfactory than the foregoing methods, afforded the monomethyl ether, m. p. 138—139° after several crystallisations from methanol.

When heated with sodium acetate and acetic anhydride on a steam-bath for 30 minutes, the monoacetate (5-acetoxy-7 : 4′-dimethoxy*iso*flavone) was obtained as diamond-shaped plates (from methanol), m. p. 202° (Found: C, 66·7; H, 4·9; OMe, 17·6. Calc. for $C_{19}H_{16}O_6$: C, 67·0; H, 4·7; 2OMe, 18·2%).

5 : 4′-*Diethoxy*-7-*methoxy*iso*flavone* (*Prunetin Diethyl Ether*) (I; R = Et).—A mixture of prunetin (0·4 g.), ethyl iodide (3 c.c.), potassium carbonate (8 g.), and acetone (100 c.c.) was heated under reflux for 18 hours. The solution was then filtered and evaporated and the oily residue shaken with N-sodium hydroxide. The insoluble solid was collected and crystallised from methanol and, after further recrystallisations from benzene–light petroleum, prunetin diethyl ether was obtained in needles, m. p. 126° (Found: C, 70·6; H, 6·0. Calc. for $C_{20}H_{20}O_5$: C, 70·5; H, 5·9%). For the product similarly prepared from 4′-ethoxy-5-hydroxy-7-methoxy-*iso*flavone Narasimhachari and Seshadri (*loc. cit.*) found m. p. 116—117°.

7 : 4′-*Dibenzyloxy*-5-*hydroxy*iso*flavone* (IV; R = R′ = CH_2Ph).—(*a*) A mixture of 5 : 7 : 4′-trihydroxy*iso*flavone (5 g.), benzyl chloride (8 c.c.), anhydrous sodium carbonate (15 g.), and sodium iodide (0·5 g.) in acetone (200 c.c.) was heated under reflux for 48 hours. When the solid had been removed, the acetone solution was concentrated to 20 c.c. and mixed with methanol (20 c.c.); the precipitate which slowly separated was then combined with the residue of sodium salts from the benzylation, and the whole shaken with dilute aqueous sodium hydroxide. The insoluble product was crystallised from acetone which deposited 7 : 4′-*dibenzyloxy*-5-*hydroxy*iso*flavone* as very faintly yellow crystals (3·8 g.), m. p. 196°. For analysis the compound was recrystallised from benzene and formed shining rectangular plates, m. p. 197° (Found: C, 77·3; H, 4·6. $C_{29}H_{22}O_5$ requires C, 77·3; H, 4·9%). An alcoholic solution gave a red colour with ferric chloride.

(*b*) The 5 : 7 : 4′-trihydroxy*iso*flavone (2·5 g.) and benzyl chloride (5 c.c.) were mixed with a solution of sodium (0·5 g.) in dry ethanol (25 c.c.). After boiling under reflux for 3 hours, the mixture was diluted with water, and the excess of benzyl chloride removed by steam-distillation. The sticky solid was collected and dissolved in boiling alcohol (15 c.c.). The product which separated on cooling was treated with N-sodium hydroxide, and the solid which remained undissolved was recovered, dried, and recrystallised from benzene. The dibenzyl ether (1·07 g.) had m. p. and mixed m. p. 197°.

Acetylation with sodium acetate and boiling acetic anhydride for 30 minutes and treatment with water gave 5-*acetoxy*-7 : 4′-*dibenzyloxy*iso*flavone* which crystallised from methanol and from benzene–light petroleum in minute needles, m. p. 197—198° (Found: C, 76·0; H, 5·0. $C_{31}H_{24}O_6$ requires C, 75·6; H, 4·9%).

7 : 4′-*Dibenzyloxy*-5-*methoxy*iso*flavone* (III; R = CH_2Ph).—The dibenzylhydroxy*iso*flavone (3·8 g.) was methylated with methyl iodide (5 c.c.) and potassium carbonate (15 g.) in acetone (150 c.c.) under reflux for 24 hours. The filtered solution was evaporated and the solid obtained after the addition of water was crystallised from ethanol (yield, 3·4 g.; m. p. 163°). Crystallisation from benzene–light petroleum or acetone–methanol gave 7 : 4′-*dibenzyloxy*-5-*methoxy*-iso*flavone* as prisms, m. p. 164° (Found: C, 77·6; H, 5·3; OMe, 7·1. $C_{30}H_{24}O_5$ requires C, 77·6; H, 5·2; OMe, 6·7%).

7 : 4′-*Dihydroxy*-5-*methoxy*iso*flavone* (III; R = H).—A solution of the dibenzyloxymethoxy-*iso*flavone (3·3 g.) in acetic acid (200 c.c.) and concentrated hydrochloric acid (100 c.c.) was heated on a steam-bath for 1½ hours. When cooled and neutralised with aqueous sodium hydroxide it gave a precipitate of 7 : 4-*dihydroxy*-5-*methoxy*iso*flavone* which crystallised from methanol in needles (1·7 g.), m. p. after previous darkening, 302° (Found: C, 67·7; H, 4·6; OMe, 10·4. $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·3; OMe, 10·9%). An alcoholic solution of the *iso*flavone with ferric chloride was coloured yellow. By heating the compound with sodium acetate and acetic anhydride at 100° for 30 minutes, 7 : 4′-*diacetoxy*-5-*methoxy*iso*flavone* was obtained, and it crystallised from methanol or benzene–light petroleum in shining rectangular plates, m. p. 169·5° (Found: C, 65·1; H, 4·6; OMe, 8·2. $C_{20}H_{16}O_7$ requires C, 65·2; H, 4·4; OMe, 8·4%).

7-*Benzyloxy*-5-*hydroxy*-4′-*methoxy*iso*flavone*.—Biochanin-A (2 g.) and benzyl chloride (3 c.c.) were added to a solution of sodium (0·2 g.) in ethanol (15 c.c.) which was then heated under reflux for 2 hours. After dilution with water and steam-distillation, the residual liquid was made alkaline with 2N-sodium hydroxide (10 c.c.). The remaining solid was collected, washed with alcohol, and crystallised from acetone–methanol. 7-*Benzyloxy*-5-*hydroxy*-4′-*methoxy*-iso*flavone* (1·2 g.) was thus obtained in pale cream-coloured plates, m. p. 190° (Found : C, 73·7; H, 4·8. $C_{23}H_{18}O_5$ requires C, 73·8; H, 4·8%).

7-*Benzyloxy*-5 : 4′-*dimethoxy*iso*flavone*.—The foregoing monohydroxy*iso*flavone (0·95 g.) was methylated in acetone with methyl iodide and potassium carbonate in the customary way, and after one crystallisation from ethanol the resulting 7-*benzyloxy*-5 : 4′-*dimethoxy*iso*flavone* (0·7 g.) had m. p. 148°. By further crystallisations from methanol–acetone and ethanol it was obtained in prisms, m. p. 150° (Found : C, 74·5; H, 5·1; OMe, 16·6. $C_{24}H_{20}O_5$ requires C, 74·2; H, 5·2; 2OMe, 16·0%).

5 : 4′-*Dimethoxy*-7-*hydroxy*iso*flavone*.—The dimethoxybenzyl ether (0·5 g.) was heated on a steam-bath with acetic acid (25 c.c.) and concentrated hydrochloric acid (12 c.c.) for 80 minutes. The cooled solution was neutralised with aqueous sodium hydroxide, and the precipitate collected and crystallised from acetone–methanol. 5 : 4′-Dimethoxy-7-hydroxy*iso*flavone separated in faintly pink prisms (0·15 g.), m. p. 294°. Walz (*loc. cit.*) records m. p. 290—293° (Found : C, 68·5; H, 4·7; OMe, 20·9. Calc. for $C_{17}H_{14}O_5$: C, 68·4; H, 4·7; 2OMe, 20·8%).

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