928. *The Chemistry of Extractives from Hardwoods. Part X.* The Constitution of Ferreirin and of Homoferreirin.*

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Ferreirin and homoferreirin, which are present in the heartwood of *Ferreirea spectabilis*, are respectively 5 : 7 : 2′-trihydroxy-4′-methoxy- and 5 : 7-dihydroxy-2′ : 4′-dimethoxy*iso*flavanone, thus being the first simple *iso*flavanones to be encountered in Nature.

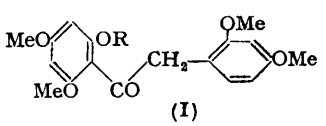
THE isolation of two new phenols, ferreirin, $C_{16}H_{14}O_6$, and homoferreirin, $C_{17}H_{16}O_6$, from the heartwood of *Ferreirea spectabilis* has already been recorded.* Ferreirin, which contains one methoxyl group, yielded first a dimethyl ether and on prolonged methylation a trimethyl derivative, thus reacting as a trihydric phenol with one hydroxyl group masked by chelation. It gave a colour reaction when reduced by sodium amalgam which was not obtained with magnesium and hydrochloric acid, and therefore appeared to be a trihydroxy-methoxy-flavone or -*iso*flavone (Briggs and Locker, *J.*, 1949, 2157). However, the molecular formula of ferreirin contains two hydrogen atoms more than are present in compounds of this constitution, and, since a flavanone structure is excluded by the absence of a colour reaction on reduction under acid conditions, these observations led to the conclusion that ferreirin is a dihydro*iso*flavone (*iso*flavanone). When preliminary experiments on the degradation of ferreirin and of its trimethyl ether by alkali fusion were unsuccessful, attempts were made to effect dehydrogenation to the corresponding *iso*flavone. This was accomplished with trimethylferreirin, $C_{19}H_{20}O_6$, by using palladised charcoal at 250°, or selenium dioxide, the product having the composition $C_{19}H_{18}O_6$. The oxidation of substituted flavanones to flavones with selenium dioxide has been described by Mahal, Rai, and Venkataraman (*J.*, 1935, 866) but the catalytic dehydrogenation method does not hitherto appear to have been used in the flavone or *iso*flavone series. The *iso*flavone structure of the compound $C_{19}H_{18}O_6$ was demonstrated by alkali hydrolysis to formic acid and a product, $C_{18}H_{20}O_6$, which in its reaction with 2 : 4-dinitrophenylhydrazine and its weakly phenolic properties behaved as an *o*-hydroxyphenyl ketone. Afterwards, this ketone was also obtained by prolonged hydrolysis of trimethylferreirin, presumably with the liberation of formaldehyde which, however, was not detected.

With concentrated nitric acid trimethylferreirin yielded 2 : 4-dimethoxy-5-nitrobenzoic acid which was identified by synthesis, and it then became evident that two of the methoxyl groups in trimethylferreirin were at positions 2′ and 4′, while a third, corresponding to the chelated hydroxyl of ferreirin, occupied the 5-position. The natural occurrence of the *iso*-flavanone with the phloroglucinol derivatives naringenin and biochanin-A (see Part IX) was assumed to denote a similar orientation of hydroxyl groups in ferreirin, whence it follows that the compound $C_{18}H_{20}O_6$ is 2 : 4-dimethoxybenzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone (I; R = H). These conclusions were largely confirmed by a synthesis of 2 : 4-dimethoxybenzyl 2 : 4 : 6-trimethoxyphenyl ketone (I; R = Me) which was identical with the methyl ether of the hydrolysis product $C_{18}H_{20}O_6$. The intermediate 2 : 4-dimethoxyphenylacetic acid was prepared by Kindler's modification of the Willgerodt reaction (*Org. Reactions*, 1946, **3**, 83) from 2 : 4-dimethoxyacetophenone, the intermediate thiomorpholide being hydrolysed without isolation; the acid chloride was then condensed with 2 : 4 : 6-trimethoxybenzene in ether containing aluminium chloride.

The recognition of the ketone $C_{18}H_{20}O_6$ as (I; R = H) simultaneously showed trimethylferreirin to be 5 : 7 : 2′ : 4′-tetramethoxy*iso*flavanone. This compound was synthesised from the pentamethoxy-ketone (I; R = Me) which was first demethylated with aluminium chloride in warm ether to 2 : 4-dimethoxybenzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone (I; R = H) identical with the principal hydrolysis product of trimethylferreirin. Condensation with ethyl formate and sodium readily gave the tetramethoxy-*iso*flavone (II), and by catalytic reduction the *iso*flavanone trimethylferreirin was obtained.

* Part IX, *J.*, 1952, 4580.

The position of the methoxyl group in ferreirin was determined in the usual manner, namely, by permanganate oxidation of ferreirin diethyl ether (III; R = Et), the presence of the 5-hydroxyl group ensuring ready attack by the reagent. An *O*-ethyl-*O*-methyl-β-resorcylic acid was thereupon isolated, but, since neither of the possible products was then known, its identification necessitated a synthesis of the two isomers. 4-Ethoxy-2-methoxybenzoic acid was obtained by ethylation of β-resorcylic acid followed by methylation of the resulting 4-ethyl ether, and the 2-ethoxy-4-methoxy-acid by reversing this procedure. In this way the oxidation product was recognised as 2-ethoxy-4-methoxybenzoic acid, whence it is apparent that ferreirin is 5 : 7 : 2′-trihydroxy-4′-methoxy*iso*flavanone (III; R = H).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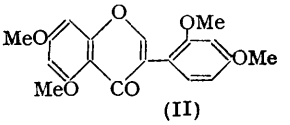
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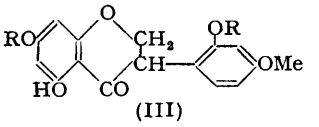
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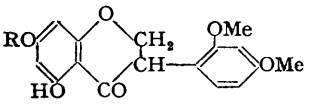

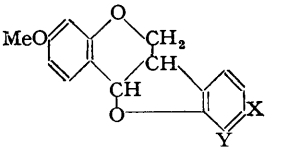
(V)

The close relationship between ferreirin and homoferreirin has already been shown (Part I) by their methylation to the same tetramethyl compound now known to be 5 : 7 : 2′ : 4′-tetramethoxy*iso*flavanone; furthermore, with diazomethane, homoferreirin affords a monomethyl derivative identical with ferreirin dimethyl ether (III; R = Me). The structure of homoferreirin was elucidated by partial alkylation to ethylhomoferreirin which when oxidised by permanganate gave 2 : 4-dimethoxybenzoic acid. It was then obvious that homoferreirin is 5 : 7-dihydroxy-2′ : 4′-dimethoxy*iso*flavanone (IV; R = H), its mono-methyl and -ethyl ethers being (IV; R = Me and Et respectively).

The occurrence of the simple *iso*flavanone nucleus has not previously been observed in Nature, and existing members of the group, excepting the more condensed derivatives found in derris root, are synthetic compounds obtained by the reduction of *iso*flavones. The presence of the 2′-hydroxyl group in ferreirin, however, suggests a possible connexion with certain extractives from the insoluble redwoods (principally *Pterocarpus* spp.), since reductive condensation of the named substituent with the carbonyl group would result in a tetracyclic system shown by McGookin, Robertson, and Whalley (*J.*, 1940, 787) to exist in the colourless constituents pterocarpin (V; methylenedioxy at X and Y) and homopterocarpin (V; methoxy at X).

Experimental

*5-Hydroxy-7 : 2′ : 4′-trimethoxy*iso*flavanone* (*Dimethylferreirin*) (III; R = Me).—Ferreirin (1 g.), heated under reflux for 8 hours in acetone with methyl sulphate (0·6 c.c., 2·1 mols.) and potassium carbonate, gave *dimethylferreirin*, which crystallised from methanol in needles (0·3 g.), m. p. 119—120° (Found: C, 65·1; H, 5·3; OMe, 27·4. $C_{18}H_{18}O_6$ requires C, 65·4; H, 5·5; 3OMe, 28·1%). The dimethyl ether (0·5 g.) was also prepared from a solution of ferreirin (1 g.) in methanol by the action of ethereal diazomethane followed by chromatographic purification in benzene on alumina. It was insoluble in aqueous alkalis and gave a brown-violet ferric reaction. The *acetate*, prepared with sodium acetate–acetic anhydride, crystallised from ethyl acetate–light petroleum in rhombs, m. p. 194—195° (Found: C, 64·4; H, 5·4; OMe, 24·7. $C_{20}H_{20}O_7$ requires C, 64·5; H, 5·4; 3OMe, 24·9%). Identical products were obtained from homoferreirin.

Limited heating with acetic anhydride–sodium acetate converted homoferreirin into *7-acetoxy-5-hydroxy-2′ : 4′-dimethoxy*iso*flavanone* which crystallised from ethyl acetate–light petroleum in plates, or from methanol in needles, m. p. 145—146° (Found: C, 63·6; H, 5·0; OMe, 17·3. $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·1; 2OMe, 17·3%). The acetate gave a brown-violet ferric colour.

5 : 7 : 2′ : 4′-*Tetramethoxy*iso*flavanone* (*Trimethylferreirin*).—Ferreirin or dimethylferreirin in acetone with excess of methyl sulphate and potassium carbonate (24 hours) yielded *trimethylferreirin*, needles (from benzene), m. p. 163° (Found: C, 66·8; H, 6·0; OMe, 36·5. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·85; 4OMe, 36·0%).

Whereas ferreirin gave oxalic acid as the only insoluble product of oxidation in aqueous alkaline permanganate at room temperature, trimethylferreirin was almost entirely unaffected by potassium permanganate in boiling acetone for 15 hours.

7 : 2′-*Diethoxy*-5-*hydroxy*-4′-*methoxy*iso*flavanone* (*Diethylferreirin*) (III; R = Et).—Ferreirin (3 g.) was refluxed in acetone with potassium carbonate and ethyl sulphate (2·7 g., 2·1 mols.) for 3 hours. The product after crystallisation from benzene consisted of *diethylferreirin*, needles (1·8 g.), m. p. 127—128° (Found: C, 67·4; H, 6·5. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·2%), insoluble in aqueous alkalis and giving a brown-violet ferric reaction.

Dehydrogenation of Trimethylferreirin to 5 : 7 : 2′ : 4′-*Tetramethoxy*iso*flavone* (II).—(a) *With palladised charcoal.* Trimethylferreirin (0·2 g.) and palladised charcoal (0·1 g.) were refluxed in Dowtherm (6 c.c.) under carbon dioxide for 7 hours. 5 : 7 : 2′ : 4′-*Tetramethoxy*iso*flavone* was obtained, after filtration, by diluting the mixture with light petroleum, and crystallised from benzene–light petroleum in needles or from methanol in rhombs (yield 0·05 g.), m. p. 203—204° (Found: C, 65·8; H, 5·2; OMe, 36·2. $C_{19}H_{18}O_6$ requires C, 65·6; H, 5·3; 4OMe, 36·2%). Reduction with sodium amalgam and acidification produced a pink coloration.

(b) *With selenium dioxide.* Trimethyferreirin (5 g.) and selenium dioxide (2 g.) were refluxed in *iso*amyl alcohol (50 c.c.) for 24 hours. The solution was filtered and the alcohol removed in steam. The product was purified by chromatography in benzene on alumina but it was necessary to reflux it in methanol with Raney nickel to eliminate the last traces of selenium compounds. The resulting *iso*flavone (II) had m. p. and mixed m. p. 203—204° (Found: C, 65·4; H, 5·0; OMe, 36·5%).

2 : 4-*Dimethoxybenzyl* 2-*Hydroxy*-4 : 6-*dimethoxybenzyl Ketone* (I; R = H).—(*a*) 5 : 7 : 2′ : 4′-Tetramethoxy*iso*flavone (1 g.) and potassium hydroxide (5·5 g.) were refluxed in alcohol (25 c.c.) and water (25 c.c.) for 1 hour. The solution was then acidified with phosphoric acid and extracted with ether, thus yielding the *ketone* (I; R = H), in rectangular plates (0·9 g.), m. p. 139°, from methanol (Found: C, 64·8; H, 6·0; OMe, 37·2. $C_{18}H_{20}O_6$ requires C, 65·0; H, 6·1; 4OMe, 37·4%). It gave a brown-red colour with ferric chloride and slowly formed a 2 : 4-dinitrophenylhydrazone precipitate with Brady's reagent. The residual acidified (Congo-red) aqueous-alcoholic solution was reduced by distillation to *ca.* 10 c.c. The distillate was neutralised with 0·1N-sodium hydroxide (required, 25 c.c.; calculated formic acid equivalent, 29·2 c.c.) and gave the usual formate tests.

(*b*) By refluxing trimethylferreirin (1 g.) in alcohol (50 c.c.) and water (10 c.c.) containing potassium hydroxide (5 g.), the ketone (I; R = H), m. p. 139°, was once more obtained (yield 0·2 g.) (Found: C, 64·9; H, 6·0; OMe, 35·5%).

(*c*) 2 : 4-Dimethoxybenzyl 2 : 4 : 6-trimethoxyphenyl ketone (I; R = Me) (0·4 g.) was heated under reflux in ether (20 c.c.) with aluminium chloride (4 g.) for 10 hours. The solid formed when the mixture was poured into water was dissolved in boiling hydrochloric acid (10 c.c.) and acetic acid (20 c.c.), whereupon dilution with water precipitated the ketone (I; R = H) (0·25 g.).

2 : 4-*Dimethoxy*-5-*nitrobenzoic Acid.*—Trimethylferreirin (2 g.) was refluxed with concentrated nitric acid (15 c.c.) for 10 minutes and the resulting solution poured into water. The precipitated solid was immediately removed and from the filtrate 2 : 4-dimethoxy-5-nitrobenzoic acid slowly separated which after crystallisation from water was obtained as fawn needles, m. p. 221° (Found: C, 47·5; H, 3·9; N, 5·8; OMe, 24·6. Calc. for $C_9H_9O_6N$: C, 47·5; H, 4·0; N, 6·2; 2OMe, 27·7%). A specimen similarly prepared from 2 : 4-dimethoxybenzoic acid had m. p. and mixed m. p. 221°; Goldstein and Jaquet (*Helv. Chim. Acta*, 1941, **24**, 30) give m. p. 220°. With diazomethane in ether–methanol both specimens of acid formed the methyl ester, m. p. 147—148·5° (lit., 147°, 150°) (Found: C, 49·9; H, 5·1; N, 5·7. Calc. for $C_{10}H_{11}O_6N$: C, 49·8; H, 4·6; N, 5·8%).

2 : 4-*Dimethoxyphenylacetic Acid.*—2 : 4-Dimethoxyacetophenone (27 g.), morpholine (26 c.c.), and sulphur (9·5 g.) were heated under reflux for 8 hours. Excess of morpholine was removed from a chloroform solution of the product with dilute hydrochloric acid, and the crude morpholide refluxed for 8 hours with sodium hydroxide (80 g.) in water (600 c.c.). The solid (10 g.) obtained by acidification gave 2 : 4-dimethoxyphenylacetic acid as needles (7·8 g.) of m. p. 111—112° when crystallised from benzene–light petroleum; Pschorr and Knoffer (*Annalen*, 1911, **382**, 56) give m. p. 113° (corr.).

The action of thionyl chloride and of phosphorus pentachloride gave resinous products, and 2 : 4-dimethoxyphenylacetyl chloride was therefore prepared from a solution of the acid (1 g.) in chloroform (8 c.c.) with phosphorus trichloride (0·4 c.c.), the mixture being warmed to 60° for 1 minute after 2 hours at room temperature. The solution was decanted from phosphorous acid and evaporated in a vacuum to leave the acid chloride as a pale yellow oil.

2 : 4-*Dimethoxybenzyl* 2 : 4 : 6-*Trimethoxyphenyl Ketone* (I; R = Me).—(*a*) 1 : 3 : 5-Trimethoxybenzene (1 g.) and aluminium chloride (1·3 g.) were dissolved in ether (20 c.c.) and treated in the cold with an ethereal solution (20 c.c.) of the acid chloride prepared from 2 : 4-dimethoxyphenylacetic acid (1 g.). After 36 hours in the refrigerator, the neutral product was isolated from the ether and purified in benzene by chromatography on alumina. The *pentamethoxyketone* (I; R = Me) crystallised from benzene in needles (0·75 g.), m. p. 110—111° (Found: C, 65·6; H, 6·1; OMe, 44·1. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4; 5OMe, 44·8%).

(*b*) 2 : 4-Dimethoxybenzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone (1 g.), obtained by alkali hydrolysis of 5 : 7 : 2′ : 4′-tetramethoxy*iso*flavone, was refluxed in acetone with methyl sulphate and potassium carbonate for 24 hours. The crystallised product (0·7 g.) (Found: C, 66·0; H, 6·1%) had m. p. 110—111° alone or mixed with the ketone (I; R = Me) of synthetic origin.

Synthesis of Trimethylferreirin.—2 : 4-Dimethoxybenzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone (1 g.) was stirred with powdered sodium (1 g.) in ethyl formate (25 c.c.) for 9 hours at 0° and then left in the cold overnight. Crushed ice was added, the excess of formate evaporated by vigorous stirring, and the product liberated by acid was taken up in benzene and the solution fractionated on alumina. The eluate crystallised from methanol in rhombs (0·25 g.), m. p. and mixed m. p. 203—204°, identical with 5 : 7 : 2′ : 4′-tetramethoxy*iso*flavone obtained by dehydrogenation of trimethylferreirin of natural origin (Found: C, 65·9; H, 5·0; OMe, 34·7%).

Hydrogenation of the *iso*flavone in acetic acid with palladised charcoal at room temperature required 24 hours. The once crystallised product consisted of trimethylferreirin, m. p. 163° (Found: C, 66·1; H, 5·7%).

Oxidation of Diethylferreirin (III; R = Et).—Diethylferreirin (1 g.) was refluxed with a saturated solution of potassium permanganate in acetone added in portions until oxidation ceased. The precipitate was then collected and dissolved in sulphurous acid and the solution extracted with ether. The sodium hydrogen carbonate-soluble fraction of the extract, after reprecipitation, crystallised from benzene–light petroleum, yielding 2-*ethoxy*-4-*methoxybenzoic acid* in needles, m. p. 114—115° (Found: C, 60·9; H, 6·0; OMe, 32·5. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2%). The *benzylthiuronium* salt separated from chloroform–light petroleum in needles, m. p. 136—137° (Found: N, 7·5. $C_{18}H_{22}O_4N_2S$ requires N, 7·7%).

2-*Ethoxy*-4-*methoxybenzoic Acid.*—2-Hydroxy-4-methoxybenzoic acid (0·8 g.) (Gomberg and Johnson, *J. Amer. Chem. Soc.*, 1917, **39**, 1687) in 2N-aqueous sodium hydroxide (20 c.c.) was vigorously stirred while ethyl sulphate (50 c.c.) was added in portions, the solution being kept alkaline with 40% sodium hydroxide. When a neutralised test portion no longer gave a ferric reaction, the mixture was heated to 100° for ½ hour, and the precipitate obtained by acidification was crystallised from water. 2-Ethoxy-4-methoxybenzoic acid (0·6 g.) separated in needles, m. p. 114—115° alone or mixed with the acid formed in the oxidation of diethylferreirin (Found: C, 61·2; H, 6·2%) [benzylthiuronium salt, m. p. and mixed m. p. 136—137° (Found: N, 7·9%)].

4-*Ethoxy*-2-*methoxybenzoic Acid.*—4-Ethoxy-2-methoxybenzoic acid (1 g.), prepared by Perkin's method (*J.*, 1895, **67**, 995), was methylated with methyl sulphate and 40% aqueous sodium hydroxide and the solution finally heated at 100°. The product thrown down by acidification gave (from benzene) rectangular plates (0·5 g.), m. p. 121°, consisting of 4-*ethoxy*-2-*methoxybenzoic acid* (Found: C, 61·1; H, 6·2%). The *benzylthiuronium* salt crystallised from chloroform in needles, m. p. 161° (Found: N, 7·8%).

7-*Ethoxy*-5-*hydroxy*-2′ : 4′-*dimethoxy*isoflavanone (*Ethylhomoferreirin*) (IV; R = Et).—Homoferreirin (0·6 g.) was refluxed in acetone with ethyl sulphate (0·3 c.c., 1·1 mol.) and potassium carbonate for 2½ hours. *Ethylhomoferreirin* (0·6 g.), which gave a brown-violet ferric reaction, crystallised from methanol in prisms, m. p. 126° (Found: C, 66·2; H, 5·7. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·9%).

Permanganate Oxidation of Ethylhomoferreirin.—The oxidation of ethylhomoferreirin (0·9 g.) was carried out as that of diethylferreirin (III; R = Et), the product isolated by ether-extraction of the sulphurous acid solution being combined with a small quantity obtained by evaporation of the acetone. Purified by reprecipitation from aqueous sodium hydrogen carbonate and crystallisation from water, the resulting acid (20 mg.) had m. p. 107—108° alone or mixed with

2 : 4-dimethoxybenzoic acid (lit., m. p. 109°) (Found : C, 59·0; H, 5·4; OMe, 33·4. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·6; 2OMe, 34%). The *benzylthiuronium* salt crystallised from chloroform in needles, m. p. 158—159° alone or with the corresponding authentic 2 : 4-dimethoxybenzoate (Found : N, 8·0. $C_{17}H_{20}O_4N_2S$ requires N, 8·0%). Similarly, the oxidation of homoferreirin afforded 2 : 4-dimethoxybenzoic acid, m. p. 107—108°.

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