354. *The Chemistry of Extractives from Hardwoods. Part VII.* Constituents of Muninga, the Heartwood of* Pterocarpus angolensis. *B: 2:4-Dihydroxyphenyl* 1-p-*Methoxyphenylethyl Ketone (Angolensin).*

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Angolensin, a further constituent of the resin extracted from the heartwood of *Pterocarpus angolensis* (*J.*, 1952, 96) and initially obtained in the form of its mono-methyl and -ethyl ethers, has been identified as 2:4-dihydroxyphenyl 1-*p*-methoxyphenylethyl ketone, a structure confirmed when later the parent natural product was isolated.

The heartwood of *Pterocarpus angolensis* contains a high proportion (19%) of alcohol-soluble material from which the previously unknown 6:4′-dihydroxy-5:7-dimethoxy*iso*flavone, muningin, was recently obtained (King, King, and Warwick, Part VI *). Attempts have since been made to isolate other crystalline constituents, for example by sublimation of the crude products obtained from the ethanolic extract through treatment with various solvents, but owing to their involatile nature the distillation of these fractions, even at low pressure, invariably resulted in extensive decomposition. The effect of methylation as a means of increasing the volatility of their phenolic components was investigated by alkylation of the benzene-soluble fraction with methyl iodide and potassium carbonate in acetone, whereupon distillation at 0·3 mm. gave a readily crystallisable product, m. p. 71°, of molecular formula $C_{17}H_{18}O_4$, containing two methoxyl groups. Nevertheless, despite the action of the methylating agent this derivative gave a positive ferric reaction and dissolved, though difficultly, in aqueous sodium hydroxide, properties which indicated the presence of a chelated phenolic hydroxyl group. The existence of this relatively inert substituent was confirmed by the preparation of two derivatives of the ether $C_{17}H_{18}O_4$, *viz.*, a liquid monoacetate and a fully methylated liquid ether, $C_{18}H_{20}O_4$.

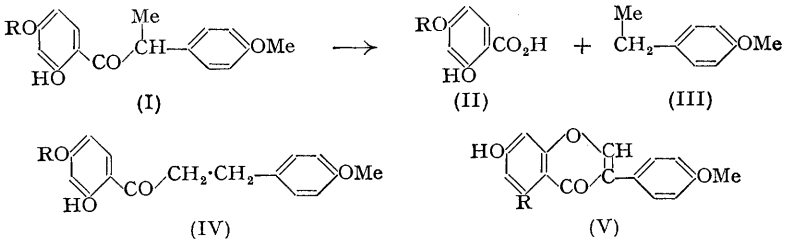
Similarly, treatment of the crude benzene-soluble fraction with ethyl iodide–potassium carbonate afforded after distillation a crystalline ether, $C_{18}H_{20}O_4$, m. p. 97°, which like the methyl compound, m. p. 71°, also exhibited the reactions of a chelated phenolic group. Since the molecular formula of the new product contains but one carbon atom more than the corresponding methyl ether, it follows that only one hydroxyl group is substituted under moderate alkylation conditions and the second methoxyl of the methyl ether, m. p. 71°, is therefore a constituent of the parent substance. To the latter the name angolensin has been given, and the ethers, m. p. 71° and 97°, were respectively termed *O*-methyl- and *O*-ethyl-angolensin.

Analytical experiments were first carried out with methylangolensin which on treatment with hot nitric acid yielded 3-nitro-*p*-anisic acid. Oxidation with potassium permanganate in acetone solution gave *p*-anisic acid and *p*-methoxyacetophenone. Fusion of methylangolensin with sodium hydroxide liberated an oil which distilled from the fusion mixture and had the properties of *p*-ethylanisole (III) (Klages, *Ber.*, 1903, **36**, 3593). It was identified by demethylation with pyridine hydrochloride to the corresponding crystalline phenol which was synthesised, and also by means of the phenylurethane of the products from both natural and synthetic sources.

When the alkali melt was dissolved in water and the solution acidified, 4-methyl-β-resorcylic acid (II; R = Me) was isolated and its identity confirmed by synthesis (Gomberg and Johnson, *J. Amer. Chem. Soc.*, 1917, **39**, 1687). These data resulted in the consideration of two structures for methylangolensin, namely (I; R = Me) and (IV; R = Me), of which, however, the former appeared more convincingly to account for the observed degradation products. Moreover, the formation of a normal acetyl derivative of methylangolensin supports this conclusion since an *o*-hydroxy-ketone of type (IV) would doubtless cyclise to a chromone under acetylation conditions, as happens for example with phloretin (see King and Robertson, *J.*, 1934, 403).

* Part VI, *J.*, 1952, 96.

The orientation of the methyl group in angolensin was ascertained by experiments with the monoethyl ether. When *O*-ethylangolensin was oxidised with potassium permanganate in acetone solution *p*-anisic acid and *p*-methoxyacetophenone were again obtained, the formation of these products at once indicating the location of the methoxylated nucleus. This was further demonstrated by alkali fusion of *O*-ethylangolensin which



(I) (II) (III)

(IV) (V)

gave *p*-ethylanisole and 4-ethyl-β-resorcylic acid (II; R = Et). Accordingly, angolensin is 2 : 4-dihydroxyphenyl 1-*p*-methoxyphenylethyl ketone (I; R = H), a structure which it was later possible to confirm when, by a method depending on its phenolic properties and ready solubility in organic solvents, the parent natural product, m. p. 117°, was isolated from the ethanolic extract, in yields approximating to 3% of the timber. The alternative formula, 2 : 4-dihydroxyphenyl 2-*p*-methoxyphenylethyl ketone (IV; R = H), was thereby finally excluded, a compound of this structure, m. p. 83°, having been described by Shinoda and Sato (*J. Pharm. Soc. Japan*, 1928, **48**, 791). Recently, angolensin was found as a crystalline deposit from the light petroleum solution obtained after very prolonged treatment of the powdered wood with this solvent in a Soxhlet apparatus (D. H. Godson and L. Jurd).

From the recognition of angolensin as (I; R = H) it follows that the liquid dimethyl derivative formed on prolonged methylation is identical with the 2 : 4-dimethoxyphenyl 1-*p*-methoxyphenylethyl ketone prepared by Wessely, Hirschel, Schlögl-Petziwal, and Prillinger (*Monatsh.*, 1938, **71**, 215) during their work on equol. Both angolensin and its methyl ether (I; R = Me) were demethylated by boiling hydriodic acid to 2 : 4-dihydroxyphenyl 1-*p*-hydroxyphenylethyl ketone.

Further fractionation of the alcoholic extract of muninga has resulted in the isolation of prunetin, 5 : 4′-dihydroxy-7-methoxy*iso*flavone (L. Jurd). The occurrence of angolensin in association with *iso*flavones (muningin, prunetin) emphasises the structural relationship of the new compound to this series of natural products, both having the same C_{15} skeleton although at different oxidation–reduction states. It is in fact possible to regard angolensin as a tetrahydro-derivative of formonetin, 7-hydroxy-4′-methoxy*iso*flavone (V; R = H), or even as a reduction product of biochanin-A, 5 : 7-dihydroxy-4′-methoxy*iso*flavone (V; R = OH), from which the oxygen atom of the pyrone ring has been removed by hydrogenolysis. Biochanin-A, which has hitherto only once been reported, occurs in germinated *Chana* grain (Siddiqui, *J. Sci. Ind. Res., India*, 1945, **4**, 68; Bose and Siddiqui *ibid.*, p. 231). It has lately been found (forthcoming publication with K. G. Neill) in the heartwood of the South American tree *Ferreirea spectabilis* where it occurs together with two *iso*flavanones.

Experimental

2-Hydroxy-4-methoxyphenyl 1-p-Methoxyphenylethyl Ketone (*O-Methylangolensin*) (I; R = Me).—After the removal of muningin from the alcoholic extract of muninga (see *J.*, 1952, 96), a portion (5 g.) of the residual dark red resin was triturated with hot benzene (2 × 100 c.c.), and the viscous material thus isolated was heated with methyl sulphate (2 c.c.) and potassium carbonate (2 g.) in acetone (50 c.c.) under reflux for 6 hours. The solution was then filtered and evaporated, and the product distilled. The pale yellow distillate (0·8 g.), b. p. 240—250° (bath temp.)/0·3 mm., largely consisted of *O-methylangolensin* which crystallised from a small volume of methanol in colourless small prisms, m. p. 71° (Found: C, 71·3; H, 6·7; OMe, 22·5; *C*-Me, 4·6. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3; OMe, 21·7; *C*-Me, 5·2%). Treatment of the crude alcoholic extract (600 g.) with benzene (3 × 4500 c.c.) followed by methylation gave a

fraction (95·2 g.), b.p. 212°/0·3 mm., from which methylangolensin (63·5 g.), m. p. 71°, was obtained, equivalent to 2% of the wood. Methylangolensin is readily soluble in organic solvents except light petroleum, and is difficultly soluble in aqueous sodium hydroxide. Its alcoholic solutions give a deep wine-red colour with ferric chloride.

A portion of the methanol solution from which distilled methylangolensin had been crystallised was evaporated, and the oily residue (5 g.) dissolved in acetone was further methylated by methyl sulphate–potassium carbonate. Distillation of the product yielded a pale straw-coloured oil (4·6 g., 88%), b. p. 190—195° (bath temp.)/0·3 mm., which gave no colour reaction with ferric chloride, and was apparently 2:4-dimethoxyphenyl 1-*p*-methoxyphenylethyl ketone [cf. Wessely, Hirschel, Schlögl-Petziwal, and Prillinger (*loc. cit.*)] (Found: C, 71·8; H, 7·1. Calc. for $C_{18}H_{20}O_4$: C, 72·0; H, 6·7%).

2 : 4-*Diacetoxyphenyl* 1-p-*Methoxyphenylethyl Ketone* (OO-*Diacetylangolensin*).—A solution in acetic anhydride of the benzene-soluble portion (0·5 g.) of the ethanol extract was boiled with anhydrous sodium acetate (0·5 g.) for 2 hours. When the mixture had been poured into water, the product, isolated by ether, was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and distilled. OO-*Diacetylangolensin* (0·52 g., corresponding to an angolensin content of 3·6% of the wood) was thus obtained as a pale straw-yellow uncrystallisable oil, b. p. 220—225° (bath temp.)/0·3 mm., readily soluble in organic solvents except light petroleum (Found: C, 67·3; H, 5·5. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·6%).

4-*Ethoxy*-2-*hydroxyphenyl* 1-p-*Methoxyphenylethyl Ketone* (O-*Ethylangolensin*) (I; R = Et).—When the benzene extract (20 g.) was refluxed for 8 hours in acetone (200 c.c.) and ethyl iodide (25 c.c.) with potassium carbonate (20 g.), and the acetone-soluble product was isolated, washed with water, and distilled, a pale yellow oil (17·1 g.), b. p. 205—218°/0·3 mm., was obtained. When dissolved in methanol it gave O-*ethylangolensin* (9 g.) as colourless hexagonal prisms, m. p. 97° (Found: C, 71·7; H, 6·7. $C_{18}H_{20}O_4$ requires C, 72·0; H, 6·7%). The compound is difficultly soluble in aqueous sodium hydroxide and gives a deep wine-red colour with ferric chloride.

The oil isolated by evaporation of the methanolic solution from which the distilled ethylangolensin had been crystallised was further treated with ethyl iodide–potassium carbonate until the ferric reaction was negative. Isolation in the usual way gave 2 : 4-*diethoxyphenyl* 1-p-*methoxyphenylethyl ketone*, an uncrystallisable oil (7·5 g.), b. p. 200—205° (bath temp.)/0·3 mm. (Found: C, 72·6; H, 7·2. $C_{20}H_{24}O_4$ requires C, 73·1; H, 7·3%).

2-*Acetoxy*-4-*methoxyphenyl* 1-p-*Methoxyphenylethyl Ketone*.—Methylangolensin (0·5 g.), m. p. 71°, was refluxed in acetic anhydride (2 c.c.) with anhydrous sodium acetate (0·5 g.) for 2 hours. The mixture was poured into water, and extraction with ether isolated the *acetyl* derivative as a colourless highly viscous oil (0·47 g., 82%), b. p. 190—195° (bath temp.)/0·3 mm. (Found: C, 69·3; H, 6·5. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%).

Oxidation of Methylangolensin.—(*a*) *With nitric acid.* Methylangolensin (1 g.) was heated with concentrated nitric acid (5 c.c.) for 1 hour on a steam-bath, and the resulting solution diluted with water. The product extracted from the aqueous solution with ether (3 × 50 c.c.) was completely soluble in aqueous sodium hydrogen carbonate; when recovered by ether extraction of the acidified carbonate solution it solidified, and crystallisation from water gave 3-nitro-*p*-anisic acid (0·45 g., 65%), m. p. and mixed m. p. 186°.

(*b*) *With potassium permanganate.* To a solution of methylangolensin (2 g.) in dry acetone (100 c.c.) heated under reflux, powdered potassium permanganate was added until the rate of oxidation became very slow. After the solvent had been evaporated, the residue was treated with water and the manganese dioxide dissolved by the passage of sulphur dioxide. The solution was then extracted with ether (3 × 50 c.c.), and the solution shaken with aqueous sodium hydrogen carbonate. Acidification of the carbonate solution and ether extraction isolated *p*-anisic acid, crystallising from water in needles, m. p. and mixed m. p. 179—181°.

The carbonate-washed ether solution was dried and evaporated, thus leaving a pale brown oil from which *p*-methoxyacetophenone (0·65 g., 62%), m. p. 33—34°, distilled at 100—105° (bath temp.)/0·3 mm. (Found: C, 71·5; H, 6·8. Calc. for $C_9H_{10}O_2$: C, 72·0; H, 6·7%). The product gave a semicarbazone, m. p. 195° alone or mixed with an authentic specimen, and the 2 : 4-dinitrophenylhydrazone prepared in ethanolic sulphuric acid crystallised from benzene in bright red rectangular plates, m. p. 230—232° (Found: N, 16·8. Calc. for $C_{15}H_{14}O_5N_4$: N, 17·0%). Borsche and Barthenheier (*Annalen*, 1942, **553**, 254) give m. p. 233—234°.

Alkali Fusion of Methylangolensin.—From treatment for several hours with boiling 40% aqueous sodium hydroxide methylangolensin was recovered as the sodium salt. The compound

(1 g.) was therefore heated with sodium hydroxide (5 g.) and water (1 c.c.) in a copper tube for 1 hour, and the product dissolved in water which was then acidified and extracted with ether. From the ethereal solution washing with aqueous sodium hydrogen carbonate removed a crystalline acid which separated from water in needles (0·42 g., 71%) giving a purple ferric reaction and having m. p. 155—156° alone or mixed with 2-hydroxy-4-methoxybenzoic acid (Gomberg and Johnson, *loc. cit.*). From it, by methylation with methyl sulphate–aqueous sodium hydroxide, 2 : 4-dimethoxybenzoic acid, m. p. 108°, was obtained.

Distillation of the carbonate-washed and dried ethereal extract gave *p*-ethylanisole (0·4 g., 84%), an oil of characteristic odour, b. p. 100—105° (bath temp.)/13 mm. It was more conveniently isolated by heating methylangolensin (5 g.) with a mixture of sodium hydroxide (5 g.), potassium hydroxide (5 g.), and water (1 c.c.), and allowing the volatile product to distil. By redistillation, *p*-ethylanisole (η = 1·5100) was obtained in 92% yield (Found : C, 78·8; H. 8·8. Calc. for $C_9H_{12}O$: C, 79·4; H, 8·8%). Klages (*loc. cit.*) records η = 1·5094, 1·5102.

p-*Ethylphenol.*—*p*-Ethylanisole (2·3 g.) derived from methylangolensin was heated with pyridine hydrochloride (8 g.) on an oil-bath at 220° for 6 hours (cf. Prey, *Ber.*, 1941, **74,** 1219). The mixture was treated with water, and the solution extracted with ether (2 × 50 c.c.) which was then washed with hydrochloric acid. From the ethereal solution 4N-sodium hydroxide (50 c.c.) extracted the product which when liberated by acid was extracted, dried, and distilled. The distillate crystallised from light petroleum in needles, m. p. 47° alone or mixed with a synthetic specimen of *p*-ethylphenol (Found : C, 78·8; H, 8·5. Calc. for $C_8H_{10}O$: C, 78·6; H. 8·2%). Warmed in light petroleum with phenyl *iso*cyanate, the phenol gave *p*-ethylphenyl phenylcarbamate, m. p. and mixed m. p. 120°.

Oxidation of Ethylangolensin.—A solution of ethylangolensin (0·6 g.) in acetone (50 c.c.) was refluxed with powdered potassium permanganate (6 g.) for 1 hour. By the process used in the oxidation of the corresponding methyl ether, a pale yellow oil (0·23 g., 76%) was isolated and identified as *p*-methoxyacetophenone by means of the semicarbazone, m. p. 195°, and 2 : 4-dinitrophenylhydrazone, m. p. 230—232°. The carbonate-soluble oxidation product crystallised from water in needles (0·02 g., 6%), m. p. 182° alone or mixed with *p*-anisic acid.

Alkali Fusion of Ethylangolensin.—A mixture of ethylangolensin (1 g.), sodium hydroxide (5 g.), and water (1 c.c.) was heated in a copper tube under reflux for 15 minutes. *p*-Ethylanisole (0·13 g.) was then isolated by the procedure used in the corresponding experiment with methylangolensin, the distillation residue consisting of unreacted ethylangolensin (0·6 g.). The carbonate-soluble product crystallised from water (charcoal) in colourless needles (0·16 g.), m. p. 154°. Mixed with 2-hydroxy-4-methoxybenzoic acid of m. p. 156—157°, it had m. p. *ca.* 130°, but with 4-ethoxy-2-hydroxybenzoic acid, no m. p. depression was observed.

2 : 4-*Dihydroxyphenyl* 1-p-*Methoxyphenylethyl Ketone* (*Angolensin*) (I; R = H).—The very dark red brittle resin (75 g.) left after the removal of muningin from the alcoholic extract of 400 g. of powdered muninga (see *J.*, 1952, 98) was dissolved in acetone (100 c.c.), and the solution diluted with ether (300 c.c.). The precipitated solid (18 g.) was discarded and the remaining liquid shaken with N-sodium hydroxide (100 c.c.). The product liberated by hydrochloric acid from the aqueous layer was then shaken with ether (2 × 100 c.c.), the ethereal solution being decanted from a tarry residue. Evaporation of the dried ethereal solution left a semi-solid red product and this was triturated with hot benzene (2 × 250 c.c.). Evaporation of the decanted benzene solution gave a brown oil (22 g.) which partly crystallised. A portion (2 g.) of benzene-soluble product was refluxed with light petroleum (b. p. 80—100°), and the pale yellow solution concentrated and set aside overnight. The very pale brown crystalline solid which separated, together with a second crop obtained by further evaporation (total 1·6 g.), when further crystallised from light petroleum gave 2 : 4-*dihydroxyphenyl* 1-p-*methoxyphenylethyl ketone* (*angolensin*) as colourless flat prisms, m. p. 117° (Found : C, 70·5; H, 5·8; OMe, 9·9. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9; OMe, 11·4%). Angolensin is freely soluble in organic solvents except light petroleum, and dissolves readily in aqueous sodium hydroxide. It gives a deep wine-red colour with ferric chloride, green with nitric acid and a yellow solution in concentrated sulphuric acid.

Methylation with excess of ethereal diazomethane at 0° for 30 minutes and crystallisation of the product from methanol gave methylangolensin (I; R = Me), m. p. and mixed m. p. 71°. Oxidation with nitric acid at 100° gave 3-nitro-*p*-anisic acid which was isolated after the addition of water by ether extraction; the acid had m. p. and mixed m. p. 186°. Alkali fusion under the conditions used for methylangolensin gave a neutral fraction consisting of *p*-ethylanisole. The alkali-soluble product was isolated by repeated ether extraction, and consisted of a pale brown oil which when distilled (bath temp., 180—185°/13 mm.) crystallised from light petroleum in prisms, m. p. 109° undepressed on admixture of a specimen with resorcinol.

2 : 4-*Dihydroxyphenyl* 1-p-*Hydroxyphenylethyl Ketone.*—Methylangolensin (1 g.), m. p. 71°, was heated with hydriodic acid (15 c.c.; *d* 1·7) and acetic acid (5 c.c.) under reflux for 3 hours. The mixture was poured into water and the product, isolated by ether as a deep red oil, was dissolved in methanol, and the solution passed down a short column of activated alumina to remove coloured impurities.

The solvent was then evaporated and the residue triturated with water, whereupon the 2 : 4-*dihydroxyphenyl* 1-p-*methoxyphenylethyl ketone* solidified and was recrystallised from water, forming prisms (0·22 g., 25%), m. p. 139—140° (Found : C, 69·9; H, 5·7. $C_{15}H_{14}O_4$ requires C, 69·75; H, 5·4%). Repetition of the experiment with angolensin also resulted in the formation of the trihydroxy-ketone. It gave a deep wine-red colour with ferric chloride in aqueous alcoholic solution.

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