300. *The Constitution and Synthesis of Afromosin.*

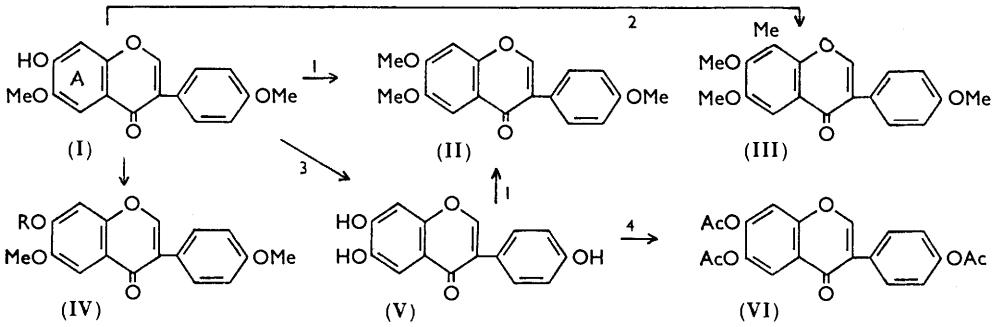
By T. B. H. McMurry and C. Y. Theng.

Afromosin, an extractive from *Afromosia elata* Harms., is shown to be the isoflavone (I), and its synthesis is described.

No work has yet been recorded on the extractives of *Afromosia elata* Harms.,[1] a West African hardwood which has become popular as a teak substitute. We have examined both light petroleum and acetone extracts.

Extraction with light petroleum affords a red oil, which on saponification gives a mono-alcohol. This may be either a triterpene alcohol or a sterol, but it has not yet been examined further since it is obtained in low yield.

The extraction with acetone affords a colourless compound, which we have called afromosin, in 0·11% yield. Afromosin, which we show below to be the isoflavone (I), contains two methoxyl groups, and a phenolic hydroxyl group. It gives a monomethyl ether (II) on methylation with diazomethane or, better, dimethyl sulphate and potassium carbonate in dry acetone. Treatment of afromosin (I) with methyl iodide and potassium carbonate in acetone affords a compound which may be an *O*-methyl-*C*-methyl derivative; presumably substitution takes place in the 8-position [2] to give compound (III). Afromosin also affords *O*-ethyl (IV; R = Et) and *O*-acetyl (IV; R = Ac) derivatives.



Reagents: 1, Me_2SO_4–K_2CO_3–$COMe_2$. 2, MeI–K_2CO_3–$COMe_2$. 3, HI–PhOH. 4, Ac_2O–C_5H_5N.

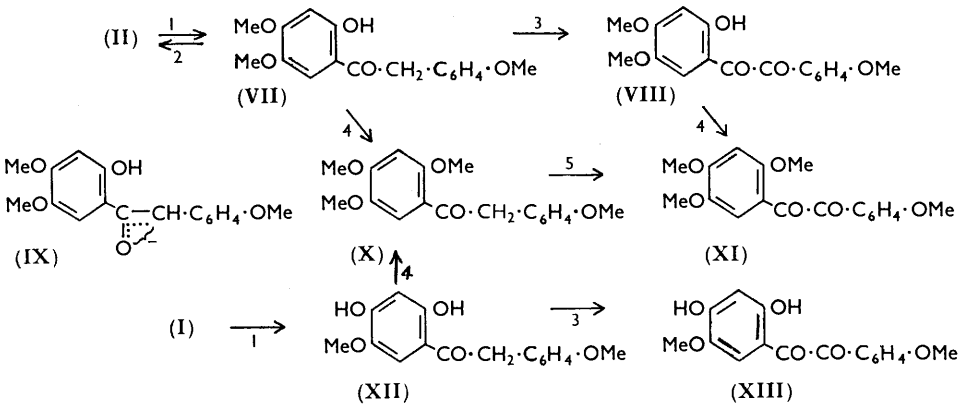
Demethylation of afromosin gives the trihydroxy-compound, $C_{15}H_{10}O_5$ (V), characterised as its triacetate (VI). Methylation of this phenol (V) affords tri-*O*-methylafromosin (II), showing that no molecular rearrangement occurs during the demethylation.[3]

These reactions suggest a flavonoid structure for afromosin, and this is supported by its bands (in Nujol) at 3200w (OH), 1635 (pyrone C=O), 1580 and 1528 (aromatic (C=C), 1255 (aromatic C–O), and 1030 cm.$^{-1}$ (OMe),[4] and ultraviolet maxima at 2580 and 3200 Å

[1] Cf. Castagne, Adriaens, and Istas, *Pubs. inst. nat. étude agron. Congo Belg., Sci. Series*, 1946, No. 3 (*Chem. Abs.*, 1948, **42**, 8467).
[2] Jain and Seshadri, *Quart. Rev.*, 1956, **10**, 169.
[3] Cf. Seshadri, *Tetrahedron*, 1959, **6**, 169.
[4] Stamm, Schmid, and Buchi, *Helv. Chim. Acta*, 1958, **41**, 2006.

(log ε 4·37 and 4·0 respectively). The relative intensities of the two peaks indicate an isoflavone rather than a flavone nucleus,[5,6] and we have confirmed this by alkaline degradation of *O*-methylafromosin (II) and of afromosin itself.

When *O*-methylafromosin is refluxed with potassium hydroxide in ethanol under nitrogen it affords the deoxybenzoin (VII), $\nu_{max.}$ 1628 (C=O), 1614, 1592, and 1514 (aromatic C=C), 1250 (aromatic C–O), and 1037 cm.$^{-1}$ (OMe)[4,6] and $\lambda_{max.}$ 2780 and 3430 Å (log ε 4·19 and 4·02 respectively).[6] This was converted into *O*-methylafromosin when heated with formanilide,[7] confirming the isoflavone skeleton. If the alkaline degradation is carried out in air, a second compound is sometimes obtained. This proved to be the benzil (VIII): it showed infrared peaks at 1677 and 1630 (C=O),[8] 1600, 1588, and 1520 (aromatic C=C), 1255 (aromatic C–O) and 1035 cm.$^{-1}$ (OMe) and has ultraviolet maxima at 2780 and 3530 Å (log ε 4·33 and 3·91 respectively).[9] It is formed by the autoxidation of the deoxybenzoin (VII) in alkaline solution, for when oxygen is passed through an alkaline solution of either *O*-methylafromosin (II) or the deoxybenzoin (VII) the benzil is formed in good yield. While a benzil has never been isolated from the alkaline degradation of an isoflavone, the autoxidation of ketones in alkali is well-known;[10,11] and, indeed, when oxygen is passed through a solution of deoxybenzoin itself and potassium t-butoxide in t-butyl alcohol, benzilic acid is formed.[11] Benzil is presumably an intermediate which rearranges in the strongly alkaline medium. The autoxidation probably involves the attack of molecular oxygen on the enolate ion (IX). Methylation of the deoxybenzoin (VII) affords the tetramethyl ether (X), which on oxidation with potassium permanganate in acetone[12] affords the tetramethoxybenzil (XI) also obtained by the methylation of (VIII). Both benzils, (VIII) and (XI), were characterised as quinoxaline derivatives.



Reagents: 1, KOH–EtOH–N_2. 2, NHPh·CHO at 250°. 3, KOH–EtOH–O_2. 4, Me_2SO_4–K_2CO_3–$COMe_2$. 5, $KMnO_4$–$COMe_2$.

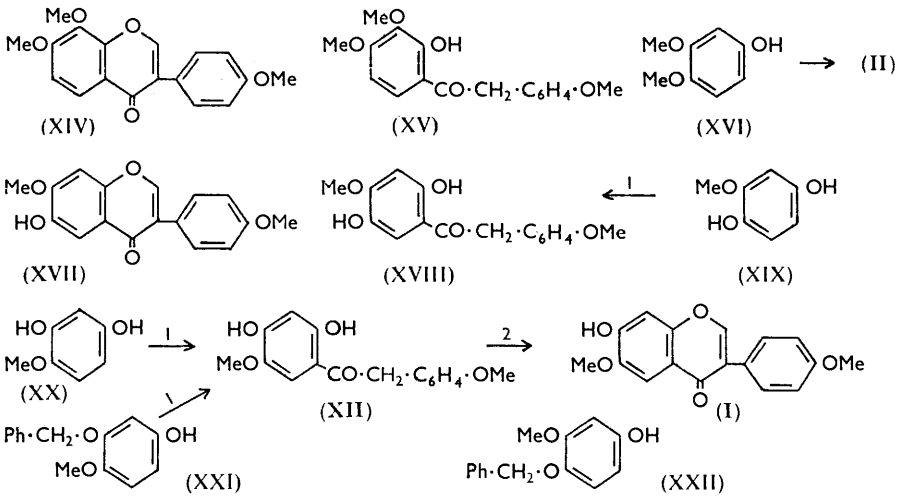
The conversion of afromosin (I) into the deoxybenzoin (XII) requires more vigorous conditions than those required for the conversion of *O*-methylafromosin (II) into the deoxybenzoin (VII). The ionisation of the 7-hydroxy-group inhibits attack of a hydroxyl ion on the pyrone ring.[13] The only product obtained when the alkaline degradation was

[5] Warburton, *Quart. Rev.*, 1954, **8**, 67.
[6] Crabbé, Leeming, and Djerassi, *J. Amer. Chem. Soc.*, 1958, **80**, 5258.
[7] Gowan, Lynch, O'Connor, Philbin, and Wheeler, *J.*, 1958, 2495.
[8] Rasmussen, Tunnicliff, and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1068; Dallwigk, Paillard, and Briner, *Helv. Chim. Acta*, 1952, **35**, 1377.
[9] Leonard, Rapala, Herzog, and Blout, *J. Amer. Chem. Soc.*, 1949, **71**, 2997; Leonard and Blout, *ibid.*, 1950, **72**, 484.
[10] Kohler and Thompson, *J. Amer. Chem. Soc.*, 1937, **59**, 887.
[11] Doering and Haines, *J. Amer. Chem. Soc.*, 1954, **76**, 482.
[12] Badcock, Cavill, Robertson, and Whalley, *J.*, 1950, 2961; Mee, Robertson, and Whalley, *J.*, 1957, 3093; Suginome, *J. Org. Chem.*, 1958, **23**, 1044.
[13] Cf. Baker and Dutt, *J.*, 1949, 2142.

carried out in a stream of oxygen was an uncharacterised oil, but the benzil (XIII) was isolated when the alkaline solution from the reaction was set aside overnight with free access to the air. Methylation of the deoxybenzoin (XII) gave its tetramethyl ether (X).

Having identified the carbon skeleton of afromosin, we turned our attention to the location of the oxygen functions. Oxidation of afromosin (I) or *O*-methylafromosin (II) with permanganate affords *p*-anisic acid, thus placing one methoxyl group in the 4'-position. The other two oxygen functions must be in ring A. However, oxidation of *O*-methylafromosin under even the mildest conditions [4] gave no fragment corresponding to ring A, but only *p*-anisic acid. However, we were able to limit the possible structures for afromosin as follows. Neither of the oxygen functions can be in the 5-position, because the positions of the short wavelength bands in the ultraviolet spectra of both afromosin (I) and the trihydroxyisoflavone (V) are unaffected by the addition of aluminium chloride: the presence of a 5-hydroxyl group causes a bathochromic shift of this peak.[14] Further, *O*-methylafromosin (II) is unaffected by aluminium chloride in anhydrous ether: a 5-methoxyl group would be demethylated; [6,15] and the trihydroxyisoflavone (V) forms a triacetate with acetic anhydride and pyridine at room temperature, whereas a 5-hydroxyl group is unaffected under these conditions.[16] The presence of an *o*-dihydroxy-system in the trihydroxyisoflavone (V) is demonstrated by the bathochromic shift of the long-wavelength band in the ultraviolet spectrum of this compound from 3260 Å (log ε 4·03) in ethanol to 3400 Å (log ε 3·97) in ethanol–boric acid–sodium acetate.[17]

The structure of *O*-methylafromosin is thus limited to (II) or (XIV), and that of the derived deoxybenzoin to (VII) or (XV). We have synthesised (VII) by the Hoesch condensation between 3,4-dimethoxyphenol (XVI) and 4-methoxybenzyl cyanide, and shown that this is identical with the degradation product from *O*-methylafromosin. The



Reagents: 1, 4-MeO·C_6H_4·CH_2·CN–$ZnCl_2$–Et_2O–HCl. 2, $Zn(CN)_2$–Et_2O–HCl.

position taken up by the entering group in the Hoesch reaction follows by analogy from the condensation of the phenol (XVI) and acetonitrile to give 2-hydroxy-3,4-dimethoxyacetophenone.[18]

Afromosin can then be either (I) or (XVII), and the derived deoxybenzoin (XII) or

[14] Harborne, *Chem. and Ind.*, 1954, 1142; Swain, *ibid.*, p. 1480.
[15] Baker and Simmonds, *J.*, 1940, 1370; Briggs and Locker, *J.*, 1950, 2379.
[16] Simonokoriyama, *Bull. Chem. Soc. Japan*, 1941, **16**, 284.
[17] Jurd, *Arch. Biochem. Biophys.*, 1956, **63**, 376; *J. Amer. Chem. Soc.*, 1958, **80**, 5531; Jurd and Rolle, *ibid.*, p. 5527.
[18] Jones, Mackenzie, Robertson, and Whalley, *J.*, 1949, 562.

(XVIII). Condensation of 4-methoxybenzyl cyanide with methoxyquinol (XIX) and 4-methoxyresorcinol (XX) affords (XVIII) and (XII) respectively. The former deoxybenzoin (XVIII) was not identical with the degradation product from afromosin, but methylation afforded the tetramethoxydeoxybenzoin (X), confirming its structure. The product from 4-methoxyresorcinol proved to be identical with the deoxybenzoin from afromosin. Reaction of the deoxybenzoin (XII) with zinc cyanide and hydrochloric acid in dry ether [19] afforded afromosin (I), thus completing the synthesis of this compound.

We have also synthesised 3-benzyloxy-4-methoxyphenol (XXI) and 4-benzyloxy-3-methoxyphenol (XXII) by oxidation of *O*-benzylisovanillin and *O*-benzylvanillin respectively with peracetic acid.[20] Hoesch condensation of the former with 4-methoxybenzyl cyanide affords the deoxybenzoin (XII).

Afromosin is one of a rare group of flavonoids lacking a 5-oxygen function.[3,21] According to biogenetic theory,[22] the formation of afromosin in Nature must involve reductive loss of a 5-oxygen function and oxidative addition of an oxygen function at the 6-position.

Experimental

Ultraviolet spectra were measured in ethanol solution with a Beckman D.U. instrument, and the infrared spectra, in Nujol (unless otherwise stated), with a Hilger 800 double-beam instrument.

Extraction of Afromosia elata *Harms.*—(a) *With light petroleum.* The powdered wood (9 kg.) was extracted with boiling light petroleum (b. p. 60—80°) for 24 hr. The deposited solid was collected at the pump, and the solvent removed from the filtrate. The residual red oil was redissolved in light petroleum, and set aside at 0° for 15 hr. The solid was collected, and the filtrate evaporated. The oily residue (17 g.) was saponified with potassium hydroxide (15 g.) in ethanol (150 c.c.) for 5 hr. The ethanol was removed and the solution extracted with ether (3 × 100 c.c.). The ethereal solution was washed with water and dried (Na_2SO_4). Removal of the ether gave an orange residue which on addition of light petroleum (b. p. 60—80°) afforded an *alcohol* (1·3 g.) as needles (from light petroleum), m. p. 135°, $[\alpha]_D^{18}$ −40·5° (*c* 1·0 in $CHCl_3$), giving a negative Liebermann–Buchard test (Found: C, 85·0; H, 11·7. $C_{27}H_{44}O$ requires C, 84·3; H, 11·5%). It formed an *acetate* (by use of acetic anhydride–pyridine), which crystallised as needles (from ethanol), m. p. 133°, $[\alpha]_D^{19}$ −44·6° (*c* 1·0 in $CHCl_3$) (Found: C, 81·4; H, 10·9. $C_{29}H_{46}O_2$ requires C, 81·7; H, 10·8%).

(b) *With acetone.* The residual wood was then extracted with acetone for 48 hr. Removal of the acetone afforded a brown residue, which on addition of acetone (150 c.c.) deposited a brown solid which was collected. More brown solid was deposited when the filtrate was concentrated. The combined solids were crystallised from ethanol, to give *afromosin* (9·5 g.) as colourless needles, m. p. 228—229° [Found: C, 68·2; H, 5·0; OMe, 20·3. $C_{15}H_8O_3(OMe)_2$ requires C, 68·4; H, 4·7; OMe, 20·8%].

O-*Methylafromosin* (II).—Afromosin (500 mg.), dimethyl sulphate (2·5 c.c.), anhydrous potassium carbonate (5·0 g.), and dry acetone (70 c.c.) were refluxed for 24 hr. The inorganic salts were collected, and the acetone was removed from the filtrate. The residue was heated with sodium hydroxide solution for 10 min., and the solid collected and crystallised from ethanol, to give O-*methylafromosin* (520 mg.) as plates, m. p. 174—175°, $\lambda_{max.}$ 2610 and 3200 Å (log ε, 4·7 and 4·3), $\nu_{max.}$ (in $CHCl_3$), 1635 (pyrone C=O), 1608, 1594, and 1518 (aromatic C=C), 1252 (aromatic C–O) and 1037 cm.$^{-1}$ (OMe) [Found: C, 68·9; H, 5·1; OMe, 29·8. $C_{15}H_7O_2(OMe)_3$ requires C, 69·2; H, 5·2; OMe, 29·8%].

Afromosin (600 mg.) was dissolved in acetone and treated with an excess of diazomethane in ether. After 60 hr. the solvents were removed. The product, crystallised several times from ethanol, gave *O*-methylafromosin (130 mg.), m. p. and mixed m. p. 172—174°.

8,O-*Dimethylafromosin* (III).—Afromosin (500 mg.) was refluxed with methyl iodide (10 c.c.) and anhydrous potassium carbonate (4·0 g.) in dry acetone (50 c.c.) for 12 hr. The product was 8,O-*dimethylafromosin* (250 mg.), which crystallised from ethanol as plates, m. p. 141°, $\lambda_{max.}$

[19] Farkas, *Chem. Ber.*, 1957, **90**, 2940.
[20] Meltzer and Doczi, *J. Amer. Chem. Soc.*, 1950, **72**, 4986.
[21] Seshadri, *Ann. Rev. Biochem.*, 1951, **20**, 491; Geissmann and Hinreiner, *Bot. Rev.*, 1952, **18**, 120.
[22] Birch, *Fortschr. Chem. org. Naturstoffe*, 1957, **14**, 186.

2580 and 3160 Å (log ε, 4·40 and 4·11 respectively), $\nu_{max.}$ 1638 (pyrone C=O), 1629, 1620, 1604, 1587, and 1508 (aromatic C=C), 1262 and 1248 (aromatic C–O) and 1031 cm.$^{-1}$ (OMe) (Found: C, 69·7; H, 5·4. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·6%).

O-*Ethylafromosin* (IV; R = Et).—Afromosin (400 mg.), ethyl iodide (6·5 c.c.), potassium carbonate (3·0 g.), and acetone (50 c.c.) were refluxed for 24 hr. The product was O-*ethylafromosin* (320 mg.), which crystallised from ethanol as needles, m. p. 135—138°, $\lambda_{max.}$ 2610 and 3120 Å (log ε 4·48 and 4·11), $\nu_{max.}$ 1624 (pyrone C=O), 1614, 1602, 1591, 1568, and 1508 (aromatic C=C), 1251 (aromatic C–O) and 1019 cm.$^{-1}$ (OMe) (Found: C, 70·0; H, 5·5. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·6%).

O-*Acetylafromosin* (IV; R = Ac).—Afromosin (480 mg.), acetic anhydride (5 c.c.), and pyridine (5 c.c.) were heated at 100° for 2 hr. The mixture was poured into water, and the resulting solid collected and crystallised from ethanol to give O-*acetylafromosin* (320 mg.) as colourless needles, m. p. 165—167°, $\lambda_{max.}$ 2570 and 3250 Å (log ε 4·48 and 4·2), $\nu_{max.}$ (in $CHCl_3$), 1765 (Ac), 1640 (pyrone C=O), 1618 and 1510 (aromatic C=C), 1250 (aromatic C–O), 1182 (acetyl), and 1034 cm.$^{-1}$ (OMe) [Found: C, 66·6; H, 4·8; OCH_3, 18·3. $C_{17}H_{10}O_4(OMe)_2$ requires C, 67·1; H, 4·75; OMe, 18·2%].

6,7,4′-*Trihydroxyisoflavone* (V).—Afromosin (300 mg.), phenol (4·5 g.), and hydriodic acid (18 c.c.) were heated at 160° for 4 hr. The mixture was cooled and poured into water. The green precipitate was collected and washed well with potassium iodide solution, followed by water. Crystallisation from methanol afforded 6,7,4′-*trihydroxyisoflavone* (120 mg.) as needles, m. p. 322° (decomp.), $\nu_{max.}$ 3260 (OH), 1635 (pyrone C=O), 1580 and 1524 (aromatic C=C), and 1253 cm.$^{-1}$ (aromatic C–O). It gave a green ferric reaction (Found: C, 66·4; H, 3·9. $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%).

6,7,4′-*Triacetoxyisoflavone* (VI).—6,7,4′-Trihydroxyisoflavone (100 mg.), acetic anhydride (0·5 c.c.), and pyridine (1·0 c.c.) were set aside at room temperature for 24 hr. The product crystallised from ethanol, to give the *triacetate* (100 mg.) as needles, m. p. 217°, $\lambda_{max.}$ 2520 and 3180 Å (log ε 4·13 and 3·31), $\nu_{max.}$ 1765, 1752, 1742, and 1196 (acetate), 1614, 1569, 1541, 1535, and 1501 (aromatic C=C) and 1260 cm.$^{-1}$ (aromatic C–O) (Found: C, 63·6; H, 4·4. $C_{21}H_{16}O_8$ requires C, 63·6; H, 4·1%).

O-*Methylafromosin from* 6,7,4′-*Trihydroxyisoflavone*.—The trihydroxyisoflavone (100 mg.), dimethyl sulphate (0·5 c.c.), potassium carbonate (1·0 g.), and dry acetone (20 c.c.) were refluxed for 24 hr. The product, isolated in the usual manner, was *O*-methylafromosin (80 mg.), m. p. and mixed m. p. 173°.

2-*Hydroxy*-4,5-*dimethoxyphenyl* 4-*Methoxybenzyl Ketone* (VII).—*O*-Methylafromosin (100 mg.), potassium hydroxide (100 mg.), ethanol (40 c.c.), and water (10 c.c.) were refluxed for 40 min. under nitrogen. The ethanol was removed, and the residue acidified. Extraction with ether gave 2-*hydroxy*-4,5-*dimethoxyphenyl* 4-*methoxybenzyl ketone* (60 mg.), which crystallised from ethanol as plates, m. p. 99—100°, giving a green ferric reaction [Found: C, 67·7; H, 6·1; OMe, 30·8. $C_{14}H_9O_2(OMe)_3$ requires C, 67·5; H, 6·0; OMe, 30·8%]. Its *oxime* crystallises from ethanol as plates, m. p. 160—161° (Found: C, 63·9; H, 6·1; N, 3·8. $C_{17}H_{19}O_5N$ requires C, 64·3; H, 6·0; N, 4·4%).

O-*Methylafromosin from* 2-*Hydroxy*-4,5-*dimethoxyphenyl* 4-*Methoxybenzyl Ketone*.—The above ketone (280 mg.) and formanilide (400 mg.) were heated at 250° for 1 hr. Crystallisation from ethanol afforded a solid (70 mg.), m. p. 174—175°, undepressed on admixture with genuine *O*-methylafromosin.

2-*Hydroxy*-4,5,4′-*trimethoxybenzil* (VIII).—(*a*) *O*-Methylafromosin (100 mg.), potassium hydroxide (1·0 g.), ethanol (40 c.c.), and water (10 c.c.) were refluxed in a stream of oxygen for 2 hr. The ethanol was removed, and the residue acidified and extracted with ether. The ethereal extract was washed with sodium hydrogen carbonate solution, and water, and then dried (Na_2SO_4). Removal of the ether afforded 2-*hydroxy*-4,5,4′-*trimethoxybenzil* (50 mg.) which crystallised as yellow needles, m. p. 137°, from ethanol [Found: C, 64·4; H, 5·8; OMe, 27·6. $C_{14}H_7O_3(OMe)_3$ requires C, 64·6; H, 5·1; OMe, 29·4%].

(*b*) Similar treatment of 2-hydroxy-4,5-dimethoxyphenyl 4-methoxybenzyl ketone (VII) (100 mg.) gave the benzil (60 mg.), m. p. and mixed m. p. 136—137°.

4-*Methoxybenzyl* 2,4,5-*Trimethoxyphenyl Ketone* (X).—2-Hydroxy-4,5-dimethoxyphenyl 4-methoxybenzyl ketone (300 mg.), dimethyl sulphate (1·5 c.c.), potassium carbonate (3·0 g.), and dry acetone (70 c.c.) were refluxed for 24 hr. The inorganic salts were collected, and the acetone was removed from the filtrate. The residue was heated for 15 min. with sodium

hydroxide solution, then extracted with ether. Removal of the ether gave 4-*methoxybenzyl* 2,4,5-*trimethoxyphenyl ketone* (210 mg.) which crystallised from ether as rhombs, m. p. 87°, $\lambda_{max.}$ 2720 and 3280 Å (log ε 4·06 and 3·94), $\nu_{max.}$ 1655 (aromatic C=O), 1607, 1581, and 1514 (aromatic C=C), 1249 (aromatic C–O) and 1028 cm.$^{-1}$ (OMe) [Found: C, 68·3; H, 6·1; OMe, 38·9. $C_{14}H_8O(OMe)_4$ requires C, 68·3; H, 6·4; OMe, 39·2%].

2,4,5,4′-*Tetramethoxybenzil* (XI).—(*a*) 4-Methoxybenzyl 2,4,5-trimethoxyphenyl ketone (80 mg.) in acetone (15 c.c.) was treated with potassium permanganate (250 mg.) in water (12 c.c.) at room temperature. When the oxidation was complete, the acetone was removed, and sulphur dioxide was passed through the solution. The solution was extracted with benzene, and the extracts were washed with aqueous sodium hydrogen carbonate and water. Removal of the benzene gave 2,4,5,4′-*tetramethoxybenzil* (40 mg.) which crystallised from ethanol as yellow rhombs, m. p. 158°, $\lambda_{max.}$ 2820 and 3450 Å (log ε 4·41 and 4·00), $\nu_{max.}$ 1666 and 1635 (C=O), 1595, 1579, and 1513 (aromatic C=C), 1257 (aromatic C–O) and 1022 cm.$^{-1}$ (OMe) [Found: C, 65·5; H, 5·5; OMe, 36·8. $C_{14}H_6O_2(OMe)_4$ requires C, 65·4; H, 5·5; OMe, 37·6%].

(*b*) 2-Hydroxy-4,5,4′-trimethoxybenzil (50 mg.), dimethyl sulphate (0·25 c.c.), potassium carbonate (500 mg.), and dry acetone (15 c.c.) were refluxed for 24 hr. The product was the tetramethoxybenzil (40 mg.), m. p. and mixed m. p. 158°.

2-(2-*Hydroxy*-4,5-*dimethoxyphenyl*)-3-p-*methoxyphenylquinoxaline*.—2-Hydroxy-4,5,4′-trimethoxybenzil (50 mg.) and freshly sublimed *o*-phenylenediamine (25 mg.) were heated at 100° for 45 min. The product crystallised from methanol to give the *quinoxaline* (40 mg.) as yellow needles, m. p. 154°, $\lambda_{max.}$ 2430, 2830, (3458), and (3850) Å [log ε 4·59, 4·40, (3·98), and (3·94) respectively] [23] (Found: C, 71·7; H, 5·2. $C_{23}H_{20}O_4N_2$ requires C, 71·1; H, 5·2%) (spectral data in parentheses refer to inflexions here and below).

2-p-*Methoxyphenyl*-3-(2,4,5-*trimethoxyphenyl*)*quinoxaline*.—2,4,5,4′-Tetramethoxybenzil (70 mg.) and *o*-phenylenediamine (35 mg.) at 100° (30 min.) gave the *quinoxaline* as yellow needles (from methanol), m. p. 174—175°, $\lambda_{max.}$ 2440, (2800), and 3570 [log ε 4·46, (4·23), and 3·92],[21] $\nu_{max.}$ 1619, 1603, 1570, 1554, 1528, and 1503 (aromatic C=C), 1240 (aromatic C–O) and 1019 cm.$^{-1}$ (OMe) [Found: C, 71·2; H, 5·7; N, 7·8; OMe, 31·4. $C_{20}H_{10}N_2(OMe)_4$ requires C, 71·6; H, 5·5; N, 7·0; OMe, 30·8%].

2,4-*Dihydroxy*-5-*methoxyphenyl* 4-*Methoxybenzyl Ketone* (XII).—Afromosin (500 mg.), potassium hydroxide (4·0 g.), ethanol (40 c.c.), and water (10 c.c.) were refluxed for 40 min. under nitrogen. The product, isolated in the usual manner, was 2,4-*dihydroxy*-5-*methoxyphenyl* 4-*methoxybenzyl ketone* (310 mg.) which was obtained in two forms (both as needles from ethanol), m. p. 118° and 128—129°, $\lambda_{max.}$ 2800 and 3480 Å (log ε 4·32 and 4·16), $\nu_{max.}$ 3400 (OH), 1642 (C=O), 1605, 1583, and 1510 (aromatic C=C), 1240 (aromatic C–O), and 1033 and 1024 cm.$^{-1}$ (OMe), giving a green ferric reaction [Found: C, 66·2; H, 5·5; OMe, 21·1. $C_{14}H_{10}O_3(OMe)_2$ requires C, 66·7; H, 5·6; OMe, 21·5%].

Methylation of the above ketone (100 mg.) with dimethyl sulphate and potassium carbonate affords 4-methoxybenzyl 2,4,5-trimethoxyphenyl ketone (X) (60 mg.), m. p. and mixed m. p. 87°.

2,4-*Dihydroxy*-5,4′-*dimethoxybenzil* (XIII).—When the alkaline solution from the alkaline degradation of afromosin (100 mg.) (see above) was set aside in an open beaker overnight, the product was 2,4-*dihydroxy*-5,4′-*dimethoxybenzil* (30 mg.) which crystallised from ethanol as yellow rhombs, m. p. 195°, $\lambda_{max.}$ 2850 and 3580 Å (log ε 4·21 and 3·87), $\nu_{max.}$ 1667 and 1650 (C=O), 1613, 1582, and 1513 (aromatic C=C), 1255 (aromatic C–O), and 1035 cm.$^{-1}$ (OMe), giving a green ferric reaction [Found: C, 63·7; H, 4·9; OMe, 20·0. $C_{14}H_8O_4(OMe)_2$ requires C, 63·6; H, 4·7; OMe, 20·5%].

p-*Anisic Acid from Afromosin Derivatives*.—(a) *From* O-*methylafromosin* (II). Potassium permanganate was added in small portions to *O*-methylafromosin (400 mg.) in acetone (50 c.c.). The mixture was refluxed, and more permanganate was added until a slight excess was present. The mixture was refluxed for a further 30 min. The precipitated manganese dioxide was collected and washed with boiling water. The combined filtrate and washings were acidified with sulphuric acid, saturated with ammonium sulphate, and extracted with ether. Removal of the ether and crystallisation of the residue from ethyl acetate–light petroleum gave *p*-anisic acid (60 mg.) as needles, m. p. and mixed m. p. 178°. The infrared spectrum of the anisic acid obtained as described above was identical with that of the genuine acid.

(b) *From afromosin*. Similar treatment of afromosin (500 mg.) gave *p*-anisic acid (40 mg.), m. p. and mixed m. p. 178°.

[23] Cf. Bohlmann, *Chem. Ber.*, 1951, **84**, 860.

Synthetic Experiments.—*2-Hydroxy-4,5-dimethoxyphenyl 4-methoxybenzyl ketone* (VII). 3,4-Dimethoxyphenol [20] (1·0 g.), 4-methoxybenzyl cyanide (2 c.c.), anhydrous zinc chloride (500 mg.), and dry ether (10 c.c.) were saturated at 0° with dry hydrogen chloride for 2 hr. The mixture was set aside at 0° for 24 hr. The ether was decanted from the resultant solid, which was washed with dry ether and then refluxed with water (30 c.c.) for 2 hr. The mixture was cooled and extracted with ether (3 × 10 c.c.). The combined ether extracts were washed with sodium hydrogen carbonate solution and then extracted with sodium hydroxide solution. The sodium hydroxide extracts were acidified with hydrochloric acid and extracted with ether. The ethereal solution was washed with water, dried (Na_2SO_4), and evaporated. The residue crystallised from ethanol, to give 2-hydroxy-4,5-dimethoxyphenyl 4-methoxybenzyl ketone (500 mg.) as needles, m. p. 99—100°, undepressed on admixture with a sample obtained by the degradation of *O*-methylafromosin

3-Benzyloxy-4-methoxyphenol (XXI). *O*-Benzylisovanillin [24] (6·0 g.) in acetic acid (120 c.c.) was treated with peracetic acid (34 c.c. of a 0·75M-solution in acetic acid) with cooling, and set aside for 15 hr. The product after removal of the acetic acid was saponified with potassium hydroxide (4·0 g.) in methanol (100 c.c.) and water (25 c.c.) for 30 min. The mixture was poured into water (300 c.c.) and extracted with ether. The aqueous layer was acidified and extracted with ether (3 × 60 c.c.). The latter extracts were combined and washed with water, and dried (Na_2SO_4), and the ether was removed. The residue crystallised to give *3-benzyloxy-4-methoxyphenol* (2·0 g.) as rhombs (from carbon tetrachloride), m. p. 86°, $\nu_{max.}$ 3600 (OH), 1605 and 1511 (aromatic C=C), 1238 (aromatic C–O), and 1022 cm.$^{-1}$ (OMe), giving a transient green ferric reaction, which rapidly became brown (Found: C, 72·0; H, 6·0. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%).

4-Benzyloxy-3-methoxyphenol (XXII). *O*-Benzylvanillin [25] (12 g.) in acetic acid (240 c.c.) was treated with peracetic acid (67 c.c. of a 0·75M-solution in acetic acid) with cooling, and set aside overnight. The product, after saponification, was *4-benzyloxy-3-methoxyphenol* (4·9 g.) which crystallised as needles, m. p. 87° (transient green ferric reaction) (Found: C, 72·3; H, 5·8%).

2,4-Dihydroxy-5-methoxyphenyl 4-methoxybenzyl ketone (XII). (*a*) 4-Methoxyresorcinol [26] (2·5 g.), 4-methoxybenzyl cyanide (5·0 c.c.), zinc chloride (500 mg.), and ether (25 c.c.) were kept saturated with hydrogen chloride at 0° for 2 hr., and the mixture was set aside at 0° for 24 hr. The product, isolated in the usual manner, was 2,4-dihydroxy-5-methoxyphenyl 4-methoxybenzyl ketone (1·05 g.), m. p. 127—128°, undepressed by a specimen of m. p. 128—129° obtained by the degradation of afromosin.

(*b*) 3-Benzyloxy-4-methoxyphenol (800 mg.), 4-methoxybenzyl cyanide (1·0 c.c.), anhydrous zinc chloride (500 mg.), and dry ether (25 c.c.) were cooled to 0° and saturated with dry hydrogen chloride for 2 hr., and set aside at 0° for 48 hr. The product was the ketone (XII) (150 mg.), m. p. and mixed m. p. 127—128°.

2,5-Dihydroxy-4-methoxyphenyl 4-methoxybenzyl ketone (XVIII). Methoxyquinol [27] (1·5 g.), 4-methoxybenzyl cyanide (3 c.c.), zinc chloride (1·0 g.), and dry ether (20 c.c.) were saturated with hydrogen chloride for 2 hr., and set aside at 0° for 15 hr. The *ketone*, isolated (750 mg.) in the usual manner, crystallised as needles (from ethanol), m. p. 150°, $\lambda_{max.}$ 2790 and 3530 Å (log ε 4·04 and 3·92), $\nu_{max.}$ 3400 (OH), 1646 (C=O), 1618 and 1509 (aromatic C=C), 1253 (aromatic C–O) and 1030 cm.$^{-1}$ (OMe) (Found: C, 67·1; H, 5·8. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%).

Methylation of this ketone (200 mg.) under the usual conditions affords 4-methoxybenzyl 2,4,5-trimethoxyphenyl ketone (150 mg.), m. p. and mixed m. p. 86—87°.

Afromosin (I).—2,4-Dihydroxy-5-methoxyphenyl 4-methoxybenzyl ketone (XII) (600 mg.), zinc cyanide (600 mg.), and anhydrous ether (10 c.c.) were saturated with dry hydrogen chloride at 0° for 1·5 hr. The mixture was set aside at 0° for 40 hr. The ether was decanted. The residual oil was washed with ether (2 × 4 c.c.), then heated with water (20 c.c.) on a water-bath for 45 min. The mixture was cooled, and the solid was collected at the pump and washed with ethanol. Recrystallisation from ethanol gave afromosin (120 mg.), m. p. and mixed m. p. 227—229°.

[24] Robinson and Sugasawa, *J.*, 1931, 3163.
[25] Kobayashi, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1927, **6**, 149.
[26] Drake, Harris, and Jaeger, *J. Amer. Chem. Soc.*, 1948, **70**, 168.
[27] Jeffreys, *J.*, 1959 2153.

The authors thank Professor W. Cocker for his interest and encouragement, Mr. E. R. Stuart for the infrared spectra, and the Government of the Republic of Ireland for a maintenance grant (to C. Y. T.).

UNIVERSITY CHEMICAL LABORATORY,
TRINITY COLLEGE, DUBLIN.

[*Received, October 19th,* 1959.]