765. *The Chemistry of Fungi. Part XLVIII.*[1] *Some Derivatives of 2,2′,4,4′-Tetrahydroxybiphenyl*

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Syntheses are described of various 3-acetyl-, 3-ethyl-, 3,3′-diacetyl-, and 3,3′-diethyl-2,2′,4,4′-tetrahydroxybiphenyls, including those obtained as degradation products from the ergot pigments, ergoflavin and ergochrysin.

The isolation of various derivatives of 2,2′,4,4′-tetrahydroxybiphenyl, as degradation products of the ergot pigments, ergoflavin and ergochrysin, has been described.[1,2] A key product from the decomposition of tetra-*O*-methylergoflavin with alkali[2] was identified as a dimethyl ether of 3,3′-diacetyl-2,2′,4,4′-tetrahydroxybiphenyl, the general structure of which was established[2] by its conversion into 3,3′-diethyl-2,2′,4,4′-tetramethoxybiphenyl, identical with an authentic specimen. This Paper records syntheses which define the orientation of the degradation phenol as (I; R = H), and of various associated derivatives.

Reduction of (I; R = H) by the Huang-Minlon process followed by ethylation gave a 3,3′-diethylbiphenyl[2] which must have one of the four alternative structures (II)—(V); these have been synthesised. Thus, 2,6-dihydroxyacetophenone (VI; R^1 = H, R^2 = COMe) was converted into 1-ethoxy-2-ethyl-4-iodo-3-methoxybenzene (VII; R^1 = Et; R^2 = Me) by way of the stages (VI; R^1 = Et, R^2 = COMe), (VI; R^1 = R^2 = Et), and (VII; R^1 = Et, R^2 = H) using standard reactions. The orientation of (VII; R^1 = Et, R^2 = Me) was defined by its conversion into 4-ethoxy-3-ethyl-2-methoxybenzoic acid (VIII; R^1 = Et; R^2 = Me, R^3 = H) by way of the Grignard reagent. An authentic specimen of this acid was prepared by successive monoethylation and monomethylation of methyl 3-ethyl-2,4-dihydroxybenzoate (VIII; R^1 = R^2 = H, R^3 = Me), followed by hydrolysis of the resultant methyl 4-ethoxy-3-ethyl-2-methoxybenzoate (VIII; R^1 = Et, R^2 = R^3 = Me). The coupling of 1-ethoxy-2-ethyl-4-iodo-3-methoxybenzene by the Ullmann process gave 4,4′-diethoxy-3,3′-diethyl-2,2′-dimethoxybiphenyl (II), which was identical with the degradation product. Hence the parent biphenyl has the orientation (I; R = H).

Similarly, 2-ethoxy-3-ethyl-1-iodo-4-methoxybenzene (VII; R^1 = Me, R^2 = Et) was prepared by way of the stages (VI; R^1 = Me, R^2 = COMe), (VI; R^1 = Me, R^2 = Et),

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[1] Part XLVII, preceding Paper.

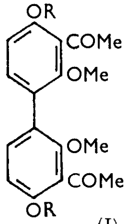
[2] G. Eglinton, F. E. King, G. Lloyd, J. W. Loder, J. R. Marshall, A. Robertson, and W. B. Whalley, *J.*, 1958, 1833.

and (VII; $R^1 = Me$, $R^2 = H$). The structure of (VII; $R^1 = Me$, $R^2 = Et$) was defined by its conversion (by way of the magnesium derivative) into 2-ethoxy-3-ethyl-4-methoxybenzoic acid (VIII; $R^1 = Me$, $R^2 = Et$, $R^3 = H$). This acid was identical with a specimen prepared by the hydrolysis of methyl 2-ethoxy-3-ethyl-4-methoxybenzoate (VIII; $R^2 = Et$, $R^1 = R^3 = Me$) which was obtained by successive monomethylation and monoethylation of methyl 3-ethyl-2,4-dihydroxybenzoate (VIII; $R^1 = R^2 = H$, $R^3 = Me$). Coupling of 2-ethoxy-3-ethyl-1-iodo-4-methoxybenzene by the Ullmann procedure gave 2,2′-diethoxy-3,3′-diethyl-4,4′-dimethoxybiphenyl (III).

The third biphenyl (IV) was obtained by the crossed Ullmann condensation of 1,3-diethoxy-2-ethyl-4-iodobenzene and 2-ethyl-4-iodo-1,3-dimethoxybenzene, a reaction which also gave 3,3′-diethyl-2,2′,4,4′-tetramethoxybiphenyl and 2,2′,4,4′-tetraethoxy-3,3′-diethylbiphenyl.

A crossed Ullmann reaction between 1-ethoxy-2-ethyl-4-iodo-3-methoxybenzene (VII; $R^1 = Et$; $R^2 = Me$) and 2-ethoxy-3-ethyl-1-iodo-4-methoxybenzene (VII; $R^1 = Me$, $R^2 = Et$) gave the fourth isomeric biphenyl, 2,4′-diethoxy-3,3′-diethyl-2′,4-dimethoxybiphenyl (V), in addition to the previously synthesised biphenyls (II) and (III). The biphenyls (II), (IV), and (V) were readily distinguishable from each other and from (II) by their melting points, mixed melting points, and infrared spectra.

The synthesis of 3,3′-diacetyl-2,2′,4,4′-tetramethoxybiphenyl (I; R = Me) was achieved by the self-coupling of 3-iodo-2,6-dimethoxyacetophenone. The Ullmann condensation of 1-iodo-2,4-dimethoxybenzene with 3-iodo-2,6-dimethoxyacetophenone gave, in addition to 2,2′,4,4′-tetramethoxybiphenyl (XII; R = H) and 3,3′-diacetyl-2,2′,4,4′-tetramethoxybiphenyl (I; R = Me), 3-acetyl-2,2′,4,4′-tetramethoxybiphenyl (XII; R = COMe), which was identical with the corresponding degradation product from ergochrysin.[1] The reduction product (XII; R = Et) of (XII; R = COMe) (cf. ref. 1) was similarly obtained from the crossed Ullmann condensation between 1-iodo-2,4-dimethoxybenzene and 2-ethyl-4-iodo-1,3-dimethoxybenzene. An alternative synthesis of 3,3′-diacetyl-2,2′,4,4′-tetramethoxybiphenyl (I; R = Me) and of the parent phenol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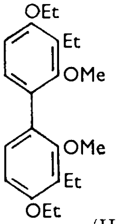
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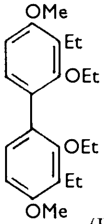
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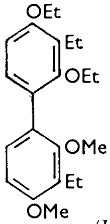
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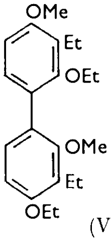
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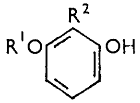
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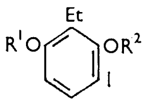
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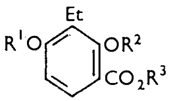
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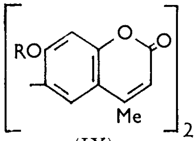
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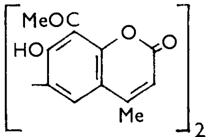
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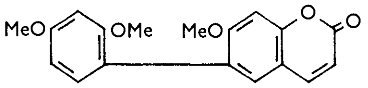
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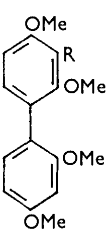
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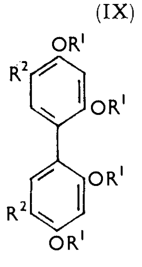
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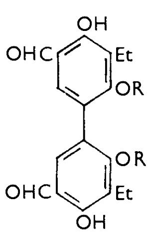
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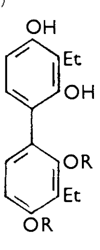
(XV)

was performed as follows. Condensation of ethyl acetoacetate with 2,2′,4,4′-tetrahydroxybiphenyl gave 6,6′-bi-(7-hydroxy-4-methylcoumarin) (IX; R = H). The di-*O*-acetate (IX; R = Ac) was subjected to a modified Fries rearrangement followed by hydrolytic removal of the coumarin rings from the crude diketone (X), to yield 3,3′-diacetyl-2,2′,4,4′-tetrahydroxybiphenyl in low yield. Methylation of a portion of the crude hydrolysate gave 3,3′-diacetyl-2,2′,4,4′-tetramethoxybiphenyl (I; R = Me) together with a second product which had the properties of 6-(2,4-dimethoxyphenyl)-7-methoxy-4-methylcoumarin (XI). Thus, the infrared spectrum had bands at 1709 (lactone), 1603, 1575, and 1555 (aromatic) cm.$^{-1}$. The nuclear magnetic resonance spectrum had signals at τ 2·54—3·5 (aromatic multiplet, 5 protons), a singlet at τ 3·84 ($>$C=C*H*–), singlets at τ 6·16, 6·17, and 6·24 (three methoxyls), and a singlet at τ 7·62 (CH_3–C=C); the proton count was 18.

Alternative approaches to the phenol (I; R = H) and its associates were designed to block the reactive 5,5′-positions in the 2,2′,4,4′-tetrahydroxybiphenyl nucleus, with readily removable groups in order to direct the acetyl residues into the 3,3′-positions. Attempts to convert 2,2′,4,4′-tetrahydroxybiphenyl into the corresponding dicarboxylic acid (XIII; R^1 = H, R^2 = CO_2H) were unsuccessful. However, the Gattermann synthesis readily furnished the dialdehyde (XIII; R^1 = H, R^2 = CHO). The orientation of this aldehyde follows from its red-brown ferric reaction in alcohol, and was defined unequivocally by its reduction and subsequent methylation to 2,2′,4,4′-tetramethoxy-5,5′-dimethylbiphenyl (XIII; R^1 = R^2 = Me) which was also obtained by the self coupling of 1-iodo-2,4-dimethoxy-5-methylbenzene. Collateral evidence for the orientation of (XIII; R^1 = R^2 = Me) and hence of (XIII; R^1 = H, R^2 = CHO) was provided by the non-identity of (XIII; R^1 = R^2 = Me) with the isomeric 2,2′,4,4′-tetramethoxy-3,3′-dimethylbiphenyl (see below). The acetate (XIII; R^1 = Ac, R^2 = CHO) was oxidised to 2,2′,4,4′-tetra-acetoxybiphenyl-5,5′-dicarboxylic acid (XIII; R^1 = Ac, R^2 = CO_2H). Various attempts to introduce acetyl residues into the 3,3′-positions of this derivative and its dimethyl ester by, *e.g.*, Fries or boron trifluoride catalysed acylations were unsuccessful.

Although 2,6-dimethoxytoluene can be oxidised to 2,6-dimethoxybenzoic acid[3] (and thence converted into the acetophenone), we failed to achieve an analogous oxidation of 2,2′,4,4′-tetramethoxy-3,3′-dimethylbiphenyl. 2,2′,4,4′-Tetramethoxybiphenyl-3,3′-dicarboxylic acid was, however, synthesised at a later stage of this investigation by the self coupling of methyl 3-iodo-2,6-dimethoxybenzoate.

In exploration of alternative routes to biphenyls of types (II)—(V), we prepared 3,3′-diethyl-2,2′,4,4′-tetrahydroxybiphenyl-5,5′-dialdehyde (XIV; R = H) in the hope that selective alkylation might yield derivatives of type (XIV; R = Alkyl). In practice, the dialdehyde (XIV; R = H) was comparatively resistant to *O*-alkylation, although small yields of, *e.g.*, 3,3′-diethyl-4,4′-dihydroxy-2,2′-dimethoxybiphenyl-5,5′-dialdehyde were obtained. Consequently, selective alkylation of 3,3′-diethyl-2,2′,4,4′-tetrahydroxybiphenyl was investigated. Surprisingly, methylation of this phenol with two molecular proportions of dimethyl sulphate gave 3,3′-diethyl-2,4-dihydroxy-2′,4′-dimethoxybiphenyl (XV; R = Me) as the only product, in high yield. Similarly, ethylation with two molcular proportions of diethyl sulphate gave 2′,4′-diethoxy-3,3′-diethyl-2,4-dihydroxybiphenyl (XV; R = Et). Methylation of (XV; R = Et) and ethylation of (XV; R = Me) gave 2′,4′-diethoxy-3,3′-diethyl-2,4-dimethoxybiphenyl (IV). Hence, the orientation of the parent di-*O*-methyl- and di-*O*-ethyl-biphenyls must be (XV; R = Me) and (XV; R = Et), respectively.

EXPERIMENTAL

Light petroleum refers to the fraction of b. p. 60—80°. Alkoxyl analyses upon mixed methyl–ethyl ethers are recorded as the total equivalent methoxyl content.

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[3] W. J. Cartwright, J. I. Jones, and D. Marmion, *J.*, 1952, 3499.

4,4′-*Diethoxy*-3,3′-*diethyl*-2,2′-*dimethoxybiphenyl* (II).—Ethylation of 2,6-dihydroxyacetophenone (10 g.) in boiling acetone (150 ml.) with diethyl sulphate (10·6 g., 1·05 mol.) and potassium carbonate (15 g.) during 6 hr. gave 2-ethoxy-6-hydroxyacetophenone which separated from benzene–light petroleum in yellow prisms (10·4 g.), m. p. 84° (Found: C, 66·5; H, 6·6. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·7%). Schmutz *et al.*[4] record m. p. 84° for a specimen prepared by an alternative method. Reduction of this ether (10 g.) with zinc amalgam (25 g.) and boiling 40% hydrochloric acid (60 ml.) was complete in 3 hr. 3-Ethoxy-2-ethylphenol was obtained as an oil, b. p. 67—70°/0·2 mm.; the p-*nitrobenzoate* formed needles, m. p. 149° (from benzene–light petroleum) (Found: C, 65·1; H, 5·4; N, 4·3. $C_{17}H_{17}NO_5$ requires C, 64·8; H, 5·4; N, 4·4%).

A solution of 3-ethoxy-2-ethylphenol (7 g.) in ethanol (100 ml.) was stirred vigorously while iodine (11·8 g.) and red mercuric oxide (6 g.) were added alternately. After 1 hr. the colour had been discharged, and 3-ethoxy-2-ethyl-6-iodophenol was isolated as an oil (8·2 g.) which could not be satisfactorily purified by distillation. The p-*nitrobenzoate* formed yellow needles, m. p. 132° (from benzene–light petroleum) (Found: C, 46·6; H, 3·9; N, 2·7. $C_{17}H_{16}INO_5$ requires C, 46·3; H, 3·7; N, 3·2%).

Methylation of this iodophenol (11·3 g.) gave 1-*ethoxy*-2-*ethyl*-4-*iodo*-3-*methoxybenzene* (7·6 g.) as a mobile oil, b. p. 92—94°/0·2 mm. [Found: C, 43·8; H, 5·0; OMe, 20·9. $C_8H_7I(OMe)(OEt)$ requires C, 43·2; H, 4·9; OMe, 20·3%].

A solution of this iodobenzene (2 g.) in ether (10 ml.) was added slowly to magnesium turnings (170 mg.) together with a crystal of iodine. The mixture was refluxed for 2 hr., cooled, treated with excess of powdered solid carbon dioxide, and decomposed by the addition of ice (100 g.) and concentrated hydrochloric acid (3 ml.). Isolated in the usual manner, 4-ethoxy-3-ethyl-2-methoxybenzoic acid (0·6 g.) formed needles, m. p. 114° (from benzene–light petroleum), identical (m. p., mixed m. p., infrared) with an authentic specimen [Found: C, 64·2; H, 7·3; OMe, 27·3. Calc. for $C_9H_8O_2(OMe)(OEt)$: C, 64·3; H, 7·2; OMe, 27·7%].

A mixture of 1-ethoxy-2-ethyl-4-iodo-3-methoxybenzene (2·3 g.) and copper bronze (6 g.) was heated at 260° for 45 min. The product was isolated from the crushed solid reaction mixture by extraction with light petroleum followed by chromatography of the extract on alumina from the same solvent. Purification from methanol gave 4,4′-diethoxy-3,3′-diethyl-2,2′-dimethoxybiphenyl (0·9 g.) in plates (prisms from light petroleum), m. p. 136° [Found: C, 73·4; H, 8·2; OMe, 35·0. Calc. for $C_{16}H_{14}(OMe)_2(OEt)_2$: C, 73·7; H, 8·4; OMe, 34·6%), identical (m. p., mixed m. p., infrared) with the product obtained from natural sources.[2]

2,2′-*Diethoxy*-3,3′-*diethyl*-4,4′-*dimethoxybiphenyl* (III).—Reduction of 2-hydroxy-6-methoxyacetophenone (4·2 g.) was effected during 3 hr. by zinc amalgam (12 g.) in boiling 40% hydrochloric acid (30 ml.). 2-Ethyl-3-methoxyphenol formed a mobile oil (2·8 g.), b. p. 82°/0·8 mm., which was characterised as the p-*nitrobenzoate*, needles, m. p. 116° (from benzene–light petroleum) (Found: C, 63·8; H, 5·0; N, 4·5. $C_{16}H_{15}NO_5$ requires C, 63·8; H, 5·0; N, 4·7%). A solution of this phenol (2·4 g.) in alcohol (30 ml.) was stirred for 1½ hr. with a mixture of red mercuric oxide (2 g.) and iodine (4 g.). 2-Ethyl-6-iodo-3-methoxyphenol formed an oil which decomposed on attempted distillation. The p-*nitrobenzoate* formed yellow needles, m. p. 159° (from methanol) (Found: C, 44·5; H, 3·3; N, 3·1. $C_{16}H_{14}INO_5$ requires C, 44·9; H, 3·3; N, 3·3%).

Ethylation of this iodophenol (15·8 g.) during 6 hr. in boiling acetone (200 ml.) containing diethyl sulphate (13·8 g.) and potassium carbonate (20 g.) gave 2-*ethoxy*-3-*ethyl*-1-*iodo*-4-*methoxybenzene* as a mobile oil (13·1 g.), b. p. 102°/0·5 mm. [Found: C, 43·8; H, 5·1; OMe, 21·1. $C_8H_7I(OMe)(OEt)$ requires C, 43·2; H, 4·9; OMe, 20·3%].

The magnesium derivative of this iodobenzene (2 g.), prepared in ether (30 ml.) containing magnesium turnings (0·17 g.), was treated with excess of powdered solid carbon dioxide, ice (100 g.), and concentrated hydrochloric acid (4 ml.). On isolation, followed by purification from acetone, 2-ethoxy-3-ethyl-4-methoxybenzoic acid formed prisms (0·9 g.), m. p. 130° [Found: C, 64·3; H, 7·4; OMe, 27·2. Calc. for $C_9H_8O_2(OMe)(OEt)$: C, 64·3; H, 7·2; OMe, 27·7%], identical (m. p., mixed m. p., infrared) with an authentic specimen.

A mixture of 2-ethoxy-3-ethyl-1-iodo-4-methoxybenzene (1·75 g.) and copper bronze (4 g.) was heated (with stirring) at 260° for ½ hr. After isolation with light petroleum followed by

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[4] J. Schmutz, R. Hirt, F. Kunzle, E. Eichenberger, and H. Lauener, *Helv. Chim. Acta*, 1953, **36**, 620.

chromatography on alumina from the same solvent, *2,2′-diethoxy-3,3′-diethyl-4,4′-dimethoxybiphenyl* formed needles (0·5 g.), m. p. 98° (from methanol or light petroleum) [Found: C, 73·5; H, 8·8; OMe, 34·7. $C_{16}H_{14}(OMe)_2(OEt)_2$ requires C, 73·7; H, 8·4; OMe, 34·6%].

Derivatives of 3-Ethyl-2,4-dihydroxybenzoic Acid.—Prepared quantitatively from 3-ethyl-2,4-dihydroxybenzoic acid [5] using ethereal diazomethane, *methyl 3-ethyl-2,4-dihydroxybenzoate* formed needles, m. p. 102° (from light petroleum) (Found: C, 61·2; H, 6·2. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2%). Methylation of this (1 g.) in boiling acetone (50 ml.) containing dimethyl sulphate (0·8 g.) and potassium carbonate (4 g.) during 2 hr. gave *methyl 3-ethyl-2-hydroxy-4-methoxybenzoate* (1 g.) in prisms, m. p. 56° (from methanol), having an intense violet ferric reaction in ethanol (Found: C, 62·8; H, 6·7. $C_{11}H_{14}O_4$ requires C, 62·8; H, 6·7%). Hydrolysis of this ester (0·5 g.) with boiling 2N-sodium hydroxide (10 ml.) and ethanol (25 ml.) gave *3-ethyl-2-hydroxy-4-methoxybenzoic* (0·4 g.) in prisms, m. p. 178° (from benzene) [Found: C, 61·4; H, 6·4; OMe, 16·1. $C_9H_9O_3(OMe)$ requires C, 61·2; H, 6·2; OMe, 15·8%].

Ethylation of methyl 3-ethyl-2-hydroxy-4-methoxybenzoate with diethyl sulphate by the acetone–potassium carbonate method gave (quantitatively) *methyl 2-ethoxy-3-ethyl-4-methoxybenzoate* as an oil, b. p. 104°/1 mm. (Found: C, 65·1; H, 8·1. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%). Hydrolysis of this ester gave 2-ethoxy-3-ethyl-4-methoxybenzoic acid from benzene–light petroleum (5 : 1) in prisms, m. p. 131°, giving no ferric reaction in ethanol [Found: C, 64·5; H, 7·4; OMe, 27·7. Calc. for $C_9H_8O_2(OMe)(OEt)$: C, 64·3; H, 7·2; OMe, 27·5%].

Monoethylation of methyl 3-ethyl-2,4-dihydroxybenzoate by the diethyl sulphate–acetone–potassium carbonate method gave *methyl 4-ethoxy-3-ethyl-2-hydroxybenzoate,* prisms, m. p. 52° (from light petroleum), having an intense violet ferric reaction in ethanol (Found: C, 64·9; H, 7·2. $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·2%). Alternatively, this ester was prepared by a modification of the method of Robinson and Shah.[6] Ethyl iodide (18·5 g.) was added to a solution of methyl 2,4-dihydroxybenzoate (4·2 g.) in methanolic potassium hydroxide (5·5 g. in 32 ml.) at 0°. The solution was vigorously agitated for ½ hr. and next day refluxed for 5 hr., when methyl 4-ethoxy-3-ethyl-2-hydroxybenzoate (1·5 g.) was isolated in the usual way.

Methylation of this ester (2 g.) by the dimethyl sulphate–acetone–potassium carbonate method gave *methyl 4-ethoxy-3-ethyl-2-methoxybenzoate* as an oil (1·75 g.), b. p. 140°/101 mm. (Found: C, 66·0; H, 7·9. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%). Hydrolysis with hot ethanolic alkali gave 4-ethoxy-3-ethyl-2-methoxybenzoic acid, needles, m. p. 115° (from benzene–light petroleum), having a negative ferric reaction in ethanol [Found: C, 64·1; H, 7·1; OMe, 27·4. Calc. for $C_9H_8O_2(OMe)(OEt)$: C, 64·3; H, 7·2; OMe, 27·5%].

2,4-Diethoxy-3,3′-diethyl-2′,4′-dimethoxybiphenyl (IV).—Ethylation of ethylresorcinol (10 g.) in boiling acetone (100 ml.) containing diethyl suphate (20 ml.) and potassium carbonate (25 g.) during 5 hr. gave *1,3-diethoxy-2-ethylbenzene* (11 g.) as a pale yellow oil, b. p. 124°/14 mm., which slowly formed prisms, m. p. *ca.* 35° [Found: C, 74·3; H, 9·6; OEt, 42·2. $C_8H_8(OEt)_2$ requires C, 73·4; H, 10·3; OEt, 42·4%]. Iodination of this ester (6 g.) with red mercuric oxide (5 g.) and iodine (9 g.) in ethanol (with stirring) occurred during 3 hr., to yield *1,3-diethoxy-2-ethyl-4-iodobenzene* as a pale yellow oil (4·5 g.), b. p. 130—132°/1 mm., which slowly formed prisms, m. p. 40° (from methanol) [Found: C, 45·1; H, 5·5; OEt, 29·3. $C_8H_7I(OEt)_2$ requires C, 45·0; OEt, 28·1%].

Prepared by the self condensation of this iodobenzene (4 g.) in the presence of copper bronze (10 g.) at 200° for 1 hr., followed by the isolation of the product with light petroleum, *3,3′-diethyl-2,2′,4,4′-tetraethoxybiphenyl* formed needles (1·5 g.), m. p. 102° (from methanol) [Found: C, 74·5; H, 9·2; OEt, 45·9. $C_{16}H_{14}(OEt)_4$ requires C, 74·6; H, 8·9; OEt, 46·6%].

A mixture of 2-ethyl-4-iodo-1,3-dimethoxybenzene [2] (2 g.), 1,3-diethoxy-2-ethyl-4-iodobenzene (2 g.) and copper bronze (10 g.) was heated at 260° for 1½ hr. The product was isolated by exhaustive extraction with light petroleum and chromatographed on alumina (30 × 1 cm.) from the same solvent, to give (i), 3,3′-diethyl-2,2′,4,4′-tetramethoxybiphenyl (0·2 g.), m. p. 109°, identical with an authentic specimen, (ii) 2,2′,4,4′-tetraethoxy-3,3′-diethylbiphenyl (0·25 g.), m. p. 102°, identical with an authentic specimen, and (iii) *2,4-diethoxy-3,3′-diethyl-2′,4′-dimethoxybiphenyl* (25 mg.) in needles, m. p. 82° (from light petroleum) [Found: C, 73·4; H, 8·6; OMe, 34·1. $C_{16}H_{14}(OMe)_2(OEt)_2$ requires C, 73·7; H, 8·4; OMe, 34·6%].

2,4′-Diethoxy-3,3′-diethyl-2′,4-dimethoxybiphenyl (V).—A mixture of 2-ethoxy-3-ethyl-1-iodo-4-methoxybenzene (3 g.), 1-ethoxy-2-ethyl-4-iodo-3-methoxybenzene (3 g.), and copper

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[5] R. D. Sprenger and P. M. Ruoff, *J. Org. Chem.*, 1946, **11**, 189.

[6] R. Robinson and R. C. Shah, *J.*, 1934, 1491.

bronze (12 g.) was heated at 260° for 1½ hr. Chromatography of an extract of the product in light petroleum from the same solvent on alumina (100 × 1 cm.) gave (i) 2,2′diethoxy-3,3′-diethyl-4,4′-dimethoxybiphenyl (1·1 g.), m. p. 98°, identical with an authentic specimen, (ii) 4,4′-diethoxy-3,3′-diethyl-2,2′-dimethoxybiphenyl (1·25 g.), m. p. 136°, identical with an authentic specimen, and (iii) 2,4′-*diethoxy*-3,3′-*diethyl*-2′,4-*dimethoxybiphenyl* (20 mg.) which formed prisms, m. p. 122° (from light petroleum) [Found: C, 73·5; H, 8·3; OMe, 34·0. $C_{16}H_{14}(OMe)_2(OEt)_2$ requires C, 73·7; H, 8·4; OMe, 34·6%]. The m. p. of this compound was depressed on admixture with the two isomeric biphenyls from fractions (i) and (ii).

3,3′-*Diacetyl*-2,2′,4,4′-*tetramethoxybiphenyl* (I; R = Me) *and Derivatives*.—(*a*) A mixture of 3-iodo-2,6-dimethoxyacetophenone [7] (2 g.) and activated copper bronze (4 g.) was kept at 235—245° for 1½ hr. After isolation with light petroleum and chromatography on alumina from the same solvent, 3,3′-diacetyl-2,2′,4,4′-tetramethoxybiphenyl (0·2 g.) formed prisms, m. p. 136°, identical with the product from natural sources.[2]

(*b*) A mixture of 1-iodo-2,4-dimethoxybenzene (2·7 g.), 3-iodo-2,6-dimethoxyacetophenone (3·1 g.), and copper bronze (4 g.) was kept at 230—240° for 1¼ hr., cooled, and extracted with light petroleum. A solution of the extract in benzene was chomatographed on alumina, giving (i) 2,2′,4,4′-tetramethoxybiphenyl (0·4 g.), m. p. 92°, (ii) 3-acetyl-2,2′,4,4′-tetramethoxybiphenyl which separated from methanol in needles (0·6 g.), m. p. 116°, identical (m. p., mixed m. p., infrared) with the product obtained by degradation of ergochrysin [1] [Found: C, 69·0; H, 6·3; OMe, 39·5. Calc. for $C_{14}H_8O(OMe)_4$: C, 68·4; H, 6·4; OMe, 39·2%], and (iii) 3,3′-diacetyl-2,2′4,4′-tetramethoxybiphenyl (0·3 g.), m. p. 136°, identical (m. p., mixed m. p., infrared) with the preparation from (*a*) above, and the product from natural sources.[2]

(*c*) A mixture of 1-iodo-2,4-dimethoxybenzene (2 g.), 2-ethyl-4-iodo-1,3-dimethoxybenzene (2 g.), and copper bronze (7·5 g.) was heated at 250—260° for 1½ hr. The light petroleum extract of the reaction mixture was chromatographed on alumina (33 × 2 cm.), and eluted with the same solvent, to yield (i) 2-ethyl-1,3-dimethoxybenzene (0·1 g.), (ii) 3,3′-diethyl-2,2′,4,4′-tetramethoxybiphenyl (0·4 g.), and (iii) 3-ethyl-2,2′,4,4′-tetramethoxybiphenyl (0·45 g.) which separated from light petroleum in prisms, m. p. 84°, identical (m. p., mixed m. p., infrared) with the product derived from ergochrysin.[1]

(*d*) Ethyl acetoacetate (5 g.) and 2,2′,4,4′-tetrahydroxybiphenyl (4·2 g.) were dissolved in sulphuric acid (16 ml.) at 0°. Next day, addition of ice (100 g.) furnished 6,6′-bi-(7-hydroxy-4-methylcoumarin) as a yellow, microcrystalline solid (4·2 g.), m. p. >350°, extremely sparingly soluble in all solvents. The crude coumarin was converted quantitatively into 6,6′-*bi*-(7-*acetoxy*-4-*methylcoumarin*) which separated in needles, m. p. 327°, when the parent compound was refluxed in a mixture of pyridine (10 ml.) and acetic anhydride (20 ml.) [Found: C, 66·6; H, 4·3; OAc, 22·0. $C_{20}H_{12}O_4(OAc)_2$ requires C, 66·4; H, 4·2; OAc, 24·8%].

A mixture of this acetate (5 g.) and powdered aluminium chloride (11·4 g.) was heated until fusion occurred (*ca.* 260°), and held at this temperature for 1¼ hr. Ice (50 g.) and 2N-hydrochloric acid (200 ml.) were added to the cooled melt; the mixture was then heated on a steam-bath for ½ hr. The solid precipitate was collected and heated (steam-bath) for 5 hr. with a solution of sodium hydroxide (8 g.) in water (40 ml.), in an atmosphere of nitrogen. Acidification of the cooled hydrolysate gave a buff solid (1·7 g.) which exhibited an intense green ferric reaction in ethanol.

A portion (0·5 g.) of the dried product, dissolved in chloroform containing 1% of acetone, was chromatographed on silica. Elution with chloroform–acetone (9 : 1) furnished 3,3′-diacetyl-2,2′,4,4′-tetrahydroxybiphenyl (25 mg.), m. p. 248—249°, identical with the product obtained by degradation of di-*O*-methylergoflavin [8] (Found: C, 64·3; H, 4·7. Calc. for $C_{16}H_{14}O_6$: C, 63·6; H, 4·7%). Another portion (0·5 g.) of the crude hydrolysate was methylated in the usual manner. The product was chromatographed on alumina from benzene, and gave 3,3′-diacetyl-2,2′,4,4′-tetramethoxybiphenyl (0·2 g.), m. p. 136°, as the major product [Found: C, 67·1; H, 6·1; OMe, 35·0. Calc. for $C_{16}H_{10}O_2(OMe)_4$: C, 67·0; H, 6·2; OMe, 34·6%]. 6-(2,4-*Dimethoxyphenyl*)-7-*methoxy*-4-*methylcoumarin*, which formed needles (15 mg.), m. p. 214° (from methanol), was a minor product [Found: C, 69·6; H, 5·5; OMe, 29·9. $C_{16}H_9O_2(OMe)_3$ requires C, 69·9; H, 5·6; OMe, 28·5%].

2,2′,4,4′-*Tetrahydroxybiphenyl*-5,5′-*dialdehyde and Derivatives*.—A mixture of 2,2′,4,4′-tetrahydroxybiphenyl (4·5 g.), hydrogen cyanide (7·5 ml.), and zinc chloride (10 g.), in ether (100 ml.),

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[7] M. V. Shah and S. Sethna, *J.*, 1959, 2676.

[8] J. W. ApSimon, J. A. Corran, N. G. Creasey, K. Y. Sim, and W. B. Whalley, *J.*, 1965, 4130.

was saturated with hydrogen chloride at 0°. Next day the crystalline product was decomposed by the addition of water (100 ml.), and the resultant solution was heated (steam-bath) for 1 hr. Purification of the crystalline precipitate gave 2,2′,4,4′-*tetrahydroxybiphenyl*-5,5′-*dialdehyde* (5 g.), needles, m. p. *ca.* 300° (decomp.) (from aqueous ethanol) (Found: C, 60·9; H, 3·8. $C_{14}H_{10}O_6$ requires C, 61·3; H, 3·7%), giving an intense red-brown ferric reaction in ethanol.

Prepared quantitatively by the usual method, 2,2′,4,4′-*tetramethoxybiphenyl*-5,5′-*dialdehyde* formed needles, m. p. 238° (from aqueous ethanol) [Found: C, 65·6; H, 5·6; OMe, 37·7. $C_{14}H_6O_2(OMe)_4$ requires C, 65·4; H, 5·5; OMe, 37·6%]. Prepared by the pyridine–acetic anhydride method, 2,2′,4,4′-*tetra-acetoxybiphenyl*-5,5′-*dialdehyde* separated from aqueous acetone in needles, m. p. 178° (Found: C, 59·6; H, 4·3; $C_{22}H_{18}O_{10}$ requires C, 59·7; H, 4·1%).

A solution of this aldehyde (1 g.) in acetone (150 ml.) containing 2N-sulphuric acid (20 ml.) was treated at 0° with a solution of potassium permanganate (1 g.) in water (25 ml.) during 8 hr. Next day, the mixture was clarified by sulphur dioxide, exhaustively extracted with ether, and the extract washed with 2N-sodium hydrogen carbonate. Acidification of these washings gave 2,2′,4,4′-*tetra-acetoxybiphenyl*-5,5′-*dicarboxylic acid* which formed needles (0·4 g.), m. p. *ca.* 300° (decomp.) (from aqueous acetone) (Found: C, 56·1; H, 4·2. $C_{22}H_{18}O_{12}$ requires C, 55·7; H, 3·8%). Prepared quantitatively with ethereal diazomethane, the *dimethyl ester* formed needles, m. p. 182° (from aqueous acetone) [Found: C, 57·7; H, 4·5; OMe, 12·3. $C_{22}H_{16}O_{10}(OMe)_2$ requires C, 57·4; H, 4·4; OMe, 12·1%].

2,2′,4,4′-*Tetramethoxy*-5,5′-*dimethylbiphenyl*.—(*a*) Reduction of 2,2′,4,4′-tetrahydroxybiphenyl-5,5′-dialdehyde (1 g.) in a boiling mixture of ethanol (20 ml.) and 50% hydrochloric acid (5 ml.) containing zinc amalgam (3 g.) was complete within 3 hr. 2,2′4,4′-*Tetrahydroxy*-5,5′-*dimethylbiphenyl* separated from the concentrated reaction liquid and formed needles (0·6 g.), m. p. 202° (from aqueous ethanol) (Found: C, 68·1; H, 5·6. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). Prepared quantitatively by methylation in the usual way, 2,2′,4,4′-*tetramethoxy*-5,5′-*dimethylbiphenyl* separated from benzene–light petroleum in prisms, m. p. 178° [Found: C, 71·6; H, 7·3; OMe, 41·5. $C_{14}H_{10}(OMe)_4$ requires C, 71·5; H, 7·3; OMe, 41·1%].

(*b*) Iodine (6·5 g.) and red mercuric oxide (3·3 g.) were added alternately during ½ hr. to a stirred solution of 2,4-dimethoxy-1-methylbenzene (3·9 g.) in ethanol (50 ml.). Isolated in the usual manner, 1-iodo-2,4-dimethoxy-5-methylbenzene formed an oil which decomposed on distillation and was used directly for the next reaction. A mixture of this iodobenzene (1·4 g.) and copper bronze (5 g.) was heated at 260° for 1 hr. An extract of the product in light petroleum was chromatographed on alumina, and gave 2,2′,4,4′-tetramethoxy-5,5′-dimethylbiphenyl (0·4 g.), prisms, m. p. 176° (from benzene–light petroleum) (Found: C, 71·7; H, 7·4. Calc. for $C_{18}H_{22}O_4$: C, 71·5; H, 7·3%), identical with that prepared by method (*a*).

2,2′,4,4′-*Tetramethoxy*-3,3′-*dimethylbiphenyl*.—Iodination of a stirred solution of 2,6-dimethoxytoluene (11 g.) in ethanol (100 ml.) by alternate addition of iodine (9 g.) and red mercuric oxide (6 g.) was complete in 2 hr. After distillation at 156°/1 mm., 1-*iodo*-2,4-*dimethoxy*-3-*methylbenzene* formed an oil (7 g.) (Found: C, 39·3; H, 4·3. $C_9H_{11}IO_2$ requires C, 38·9; H, 4·0%). Prepared by the self coupling of this iodobenzene (7 g.) in the presence of copper bronze (20 g.) at 260° during 1 hr., an extract of the product in light petroleum was chromatographed on alumina, to yield 2,2′,4,4′-*tetramethoxy*-3,3′-*dimethylbiphenyl* (2 g.), prisms, m. p. 130° (from light petroleum) [Found: C, 71·2; H, 7·4; OMe, 41·7. $C_{14}H_{10}(OMe)_4$ requires C, 71·5; H, 7·3; OMe, 41·1%].

2,2′4,4′-*Tetramethoxybiphenyl*-3,3′-*dicarboxylic Acid*.—An agitated solution of methyl 2,6-dimethoxybenzoate [9] (0·7 g.) in ethanol (8 ml.) was treated alternately with iodine (1·2 g.) and mercuric oxide (0·8 g.) during 3 hr. *Methyl* 3-*iodo*-2,6-*dimethoxybenzoate* formed prisms (0·5 g.), m. p. 87° (from methanol or light petroleum) (Found: C, 36·8; H, 3·6; I, 43·3. $C_{10}H_{11}IO_4$ requires C, 37·3; H, 3·4; I, 39·4%). The action of iodine and iodic acid upon 2,6-dihydroxybenzoic acid gave a mixture of mono- and di-iodinated products.

A mixture of methyl 3-iodo-2,6-dimethoxybenzoate (1·3 g.) and copper bronze (2 g.) was kept at 220—240° for 1 hr. Extraction of the product with chloroform and crystallisation from methanol gave *dimethyl* 2,2′,4,4′-*tetramethoxybiphenyl*-3,3′-*dicarboxylate* (0·6 g.), in prisms, m. p. 187° (Found: C, 61·0; H, 5·7. $C_{20}H_{22}O_8$ requires C, 61·5; H, 5·7%). Hydrolysis of this ester (1·1 g.) with 50% methanolic potassium hydroxide (40 ml.) on a steam-bath during

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[9] F. P. Doyle, K. Hardy, J. H. C. Nayler, M. J. Soulal, E. R. Stove, and H. R. J. Waddington, *J.* 1962, 1454.

2 hr. gave (quantitatively) 2,2′,4,4′-*tetramethoxybiphenyl*-3,3′-*dicarboxylic acid*, needles, m. p. 255° (decomp.) (from acetone–methanol) [Found: C, 59·6; H, 4·9; OMe, 34·0. $C_{14}H_6O_4(OMe)_4$ requires C, 59·7; H, 5·0; OMe, 34·2%].

3,3′-*Diethyl*-2,2′,4,4′-*tetrahydroxybiphenyl*.—Demethylation of 3,3′-diethyl-2,2′,4,4′-tetramethoxybiphenyl (4 g.) was effected during ½ hr., with a boiling hydriodic acid (*d* 1·7) (16 ml.) and acetic acid [from acetic anhydride (8 ml.)]. Purified from hot water (charcoal), 3,3′-*diethyl*-2,2′,4,4′-*tetrahydroxybiphenyl* (2 g.) formed needles, m. p. 142° (of a hydrate), which was converted into the anhydrous form, m. p. 219°, by sublimation at 200°/0·5 mm. (Found: C, 69·6; H, 6·8. $C_{16}H_{18}O_4$ requires C, 70·1; H, 6·6%).

Prepared at 0° by saturation with hydrogen chloride of a solution of the previous biphenyl in ether (100 ml.) containing hydrogen cyanide (4·5 ml.) and zinc chloride (6 g.), followed by decomposition of the aldimine complex 24 hr. later with water (100 ml.) at 100° for 1 hr., 3,3′-*diethyl*-2,2′,4,4′-*tetrahydroxybiphenyl*-5,5′-*dialdehyde* formed needles (1·5 g.), m. p. 237° (from aqueous ethanol) (Found: C, 65·2; H, 5·4. $C_{18}H_{18}O_6$ requires C, 65·4; H, 5·5%).

Methylation of this aldehyde (1 g.) with dimethyl sulphate (0·6 ml.) and potassium carbonate (5 g.) in boiling acetone (50 ml.) during 6 hr. furnished a mixture which was chromatographed on silica from benzene–light petroleum (1 : 1), to give (i) starting material (0·9 g.), and (ii) 3,3′-*diethyl*-4,4′*dihydroxy*-2,2′-*dimethoxybiphenyl*-5,5′-*dialdehyde* (10 mg.), prisms, m. p. 148° (from benzene–light petroleum) (Found: C, 67·2; H, 6·1. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·2%), giving an intense red-brown ferric reaction in ethanol and showing only chelated hydroxyl (3185b) and chelated aldehyde (1639s cm.$^{-1}$) bands in the infrared spectrum.

Methylation of 3,3′-diethyl-2,2′4,4′-tetrahydroxybiphenyl-5,5′-dialdehyde with a large excess of dimethyl sulphate in boiling methyl ethyl ketone containing potassium carbonate, during 24 hr., gave 3,3′-*diethyl*-2,2′,4,4′-*tetramethoxybiphenyl*-5,5′-*dialdehyde* in low yield, prisms, m. p. 90° (from light petroleum) [Found: C, 68·2; H, 7·0; OMe, 32·5. $C_{18}H_{14}O_2(OMe)_4$ requires C, 68·4; H, 6·8; OMe, 32·2%], giving no ferric reaction in ethanol.

Alkylation of 3,3′*Diethyl*-2,2′4,4′-*tetrahydroxybiphenyl*.—(*a*) Methylation of this biphenyl (0·5 g.) in boiling acetone (25 ml.) containing potassium carbonate (3 g.) and dimethyl sulphate (0·5 g., 2·1 mol.) during 2 hr. gave 3,3′-*diethyl*-2,4-*dihydroxy*-2′,4′-*dimethoxybiphenyl*, needles (0·4 g.), m. p. 132° (from benzene–light petroleum) [Found: C, 71·4; H, 7·5; OMe, 20·0. $C_{16}H_{16}O_2(OMe)_2$ requires C, 71·5; H, 7·3; OMe, 20·5%]. Ethylation of this biphenyl (0·25 g.) with excess of diethyl sulphate in acetone–potassium carbonate during 72 hr. gave 2,4-diethoxy-3,3′-diethyl-2′,4′-dimethoxybiphenyl (0·2 g.), needles, m. p. 82°, identical (m. p., mixed m. p., infrared) with the authentic specimen previously prepared [Found: C, 73·5; H, 8·7; OMe, 34·6. Calc. for $C_{16}H_{14}(OMe)_2(OEt)_2$: C, 73·7; H, 8·4; OMe, 34·6%].

(*b*) 3,3′-Diethyl-2,2′,4,4′-tetrahydroxybiphenyl (0·5 g.) was heated in boiling acetone (25 ml.) containing potassium carbonate (3 g.) and diethyl sulphate (0·5 ml., 2·1 mol.) during 2 hr., to give 2,4-*diethoxy*-3,3′-*diethyl*-2′,4′-*dihydroxybiphenyl* (0·38 g.), rosettes of needles, m. p. 181° (from benzene–light petroleum) [Found: C, 72·5; H, 8·1; OMe, 27·4. $C_{16}H_{16}O_2(OEt)_2$ requires C, 72·7; H, 7·9; OMe, 27·3%]. Methylation of this diethyl ether (0·5 g.) occurred during 4 hr., to yield 2,4-diethoxy-3,3′-diethyl-2′,4′-dimethoxybiphenyl (0·25 g.), m. p. 82°, identical (m. p., mixed m. p., infrared) with the fully alkylated specimen prepared in (*a*) and with the authentic specimen.

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