6. iso*Taxiresinol* * (3′-*Demethyl*iso*lariciresinol*), *a New Lignan extracted from the Heartwood of the English Yew*, Taxus baccata.

By F. E. King, L. Jurd, and T. J. King.

A hitherto unknown lignan containing three phenolic hydroxyl groups and one methoxyl group has been isolated from the heartwood of the English yew, *Taxus baccata*. In view of the identity of the methylated lignan with *iso*lariciresinol dimethyl ether (Haworth and Kelly, *J.*, 1937, 384) it has been named *iso*taxiresinol. Oxidation of the triethyl ether to 2-(3 : 4-diethoxybenzoyl)-4-ethoxy-5-methoxybenzoic acid, which has been identified by syntheses, establishes the constitution of the new compound as 3′-demethyl*iso*lariciresinol.

From the same source a *meso*inositol monomethyl ether has been obtained which has the properties of sequoyitol found in the California redwood, *Sequoia sempervirens*.

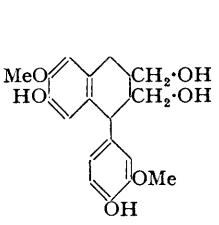
The English yew (*Taxus baccata*) is chiefly of interest for the existence in its leaves, shoots, and berries of the incompletely formulated toxic alkaloid taxine (see Henry, "The Plant Alkaloids," 4th edn., 1949, p. 769). Associated with it is taxicatin, 3 : 5-dimethoxyphenyl-D-glucoside (Lefebvre, *J. Pharm. Chim.*, 1907, iv, **26**, 241; Merz and Preuss, *Arch. Pharm. Chim.*, 1941, **279**, 134; 1943, **281**, 205), but little is known of the products of other parts of the tree, and the timber, which is classed as a softwood and stated to be highly resistant to decay, does not appear to have been hitherto subjected to chemical investigation. The felling of a large yew tree in the grounds of the University Park, Nottingham, recently afforded an opportunity of examining the heartwood constituents, and this has led to the isolation of a new phenolic lignan which for reasons evident in the ensuing discussion has been designated *iso*taxiresinol. Present also in the aqueous extract is a monomethyl *meso*inositol believed to be identical with sequoyitol, a constituent of the California redwood, *Sequoia sempervirens*.

The lignan, amounting to 1% of the undried heartwood, together with other non-crystalline material, was removed from the powdered timber with boiling water; it was then isolated by extraction of the concentrated aqueous solution with ether, the ether-soluble portion being recrystallised from ethyl acetate and finally acetic acid until the colourless *iso*taxiresinol, $C_{19}H_{22}O_6$, m. p. 171°, was obtained. The resinol contains one methoxyl group, and the formation of crystalline alkali-insoluble trimethyl and triethyl ethers on treatment with alkyl sulphate or iodide in presence of alkali indicated the existence of three phenolic hydroxyl groups. Although acyl derivatives of *iso*taxiresinol and of its trimethyl ether could not be crystallised, the alcoholic function of the two remaining oxygen atoms was apparent from the formation of a crystalline diacetate of the *O*-triethyl*iso*taxiresinol.

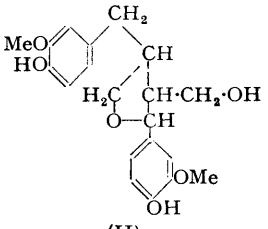
* On account of the close relationship of the new lignan to *iso*lariciresinol the name "taxiresinol" is reserved in anticipation of the possible existence of an isomer similarly related to lariciresinol.—F. E. K.

When treated with hot nitric acid, the trimethyl and triethyl ethers respectively gave 4 : 5-dinitroveratrole and 4 : 5-dinitrocatechol diethyl ether, which taking into account the molecular formula and the existence of a methoxyl group demonstrated the occurrence of both a catechol and a methoxyphenol nucleus in the molecule. Oxidation of the trimethyl ether with alkaline permanganate or potassium dichromate in acetic acid gave veratroylveratric acid. From all these data it was apparent that the new natural product was a member of the lignan group. Further consideration indicated its close connexion with *iso*lariciresinol (I) which had been obtained by Haworth and Kelly (*J.*, 1937, 384) by isomerisation of lariciresinol (II), a constituent of the resinous exudate of the larch, *Larix decidua*. The properties of the trimethyl ether of the new lignan corresponded with those of *iso*lariciresinol dimethyl ether, and a direct comparison of the two ethers and of their respective anhydro-compounds proved them to be identical. We are indebted to Professor R. D. Haworth, F.R.S., for specimens of the *iso*lariciresinol derivatives.

The new lignan having been thus shown to be a demethyl*iso*lariciresinol it merely remained to determine the relative orientation of the methoxyl and the phenolic substituents. Four alternative structures are possible, *i.e.*, with the methoxyl group occupying position 6, 7, 3′, or 4′ respectively, but two of these (methoxyl at 7 or 4′) were tentatively excluded on the grounds that no known natural product in the lignan series contains an *iso*vanillyl nucleus. Furthermore, the formation of 1 : 2-diethoxy-4 : 5-dinitrobenzene as the principal nitric acid oxidation product of *iso*taxiresinol triethyl ether is more likely with the orientation of substituents shown in (III; R = Et) than if the two ethoxy groups were attached to the tetrahydronaphthalene nucleus. These considerations, though admittedly speculative, lead to (III; R = H) as the most probable structure for *iso*taxiresinol, an expression which was subsequently deduced from the nature of the triethoxymethoxybenzophenone-2-carboxylic acid, m. p. 173·5°, resulting on oxidation of the *iso*taxiresinol triethyl ether with permanganate. The constitution of this oxidation product as (IV; R = CO_2H) was duly established by syntheses, thereby affording unequivocal confirmation of (III; R = H) as the structure of *iso*taxiresinol.



(I)



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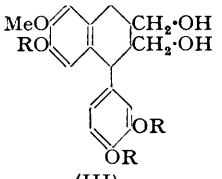

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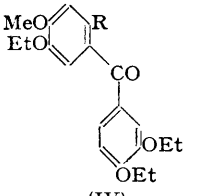
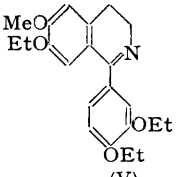
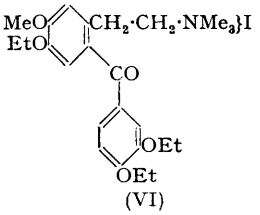


(IV)



(V)



(VI)

Early attempts to synthesise (IV; R = CO_2H) depended on the oxidation of 5 : 3′ : 4′-triethoxy-4-methoxy-2-methylbenzophenone (IV; R = Me) prepared by the condensation of 4-ethoxy-3-methoxytoluene with 3 : 4-diethoxybenzoyl chloride, but the product was unaffected by treatment with potassium permanganate under a variety of conditions. By chromium trioxide oxidation in acetic acid solution, alone or with sulphuric acid, 3 : 6 : 7-triethoxy-2-methoxyanthraquinone and a small amount of an unidentified acid were obtained. Oxidation with potassium dichromate in boiling 75% acetic acid gave a small quantity of the anthraquinone, an alkali-insoluble substance, m. p. 152°, and an acid which after

several crystallisations had m. p. 172—173° and formed a methyl ester, m. p. 110°, not depressed on admixture with the acid and ester, respectively, obtained from *iso*taxiresinol triethyl ether. Their identity thus appeared certain, but in view of the small yield and difficult purification of the oxidation product, an alternative synthesis was devised from the more readily oxidisable 5 : 3′ : 4′-triethoxy-4-methoxy-2-vinylbenzophenone (IV; R = $CH{:}CH_2$).

The necessary vinyl compound was formed by exhaustive methylation of a suitable 1-aryldihydro*iso*quinoline, for the preparation of which 2-(4-ethoxy-3-methoxyphenyl)ethylamine was condensed with 3 : 4-diethoxybenzoyl chloride giving 3 : 4-diethoxy-*N*-[2-(4-ethoxy-3-methoxyphenyl)ethyl]benzamide. 1-(3 : 4-Diethoxyphenyl)-7-ethoxy-3 : 4-dihydro-6-methoxy*iso*quinoline (V) was then obtained by ring closure of the amide with phosphoryl chloride in boiling toluene. On treating the dihydro*iso*quinoline methiodide with cold aqueous alkali and methyl iodide it was converted almost quantitatively into 2-[2-(3 : 4-diethoxybenzoyl)-4-ethoxy-5-methoxyphenyl]ethyltrimethylammonium iodide (VI), a transformation doubtless involving the usual rearrangement of a methohydroxide to a hydroxy-amine followed by ring opening to the isomeric keto-secondary base which is thereupon methylated to the quaternary salt. The various stages have been set out by Gensler and Samour (*J. Amer. Chem. Soc.*, 1950, **72**, 3318) in a summary of a parallel investigation on the synthesis of a picropodophyllin oxidation product analogous to (IV; R = CO_2H) (see also Reeve and Eareckson, *ibid.*, p. 5195), but the intermediate methiodide corresponding to (VI) was not isolated, the action of aqueous-alcoholic alkali leading directly to a vinylbenzophenone. Degradation of the methiodide (VI) was accomplished by heating it with aqueous alkali, the resulting vinylbenzophenone (IV; R = $CH{:}CH_2$) being oxidised by potassium permanganate in boiling acetone to the acid (IV; R = CO_2H). Both the acid and its methyl ester were indistinguishable from the corresponding products derived from the natural triethyl ether (III; R = Et), thus confirming the structure (III; R = H) attributed on general grounds to *iso*taxiresinol.

*iso*Lariciresinol (I) to which the new lignan is so closely analogous, appears to be known solely as a transformation product of the naturally occurring lariciresinol (II) (Haworth and Kelly, *loc. cit.*). Owing to the nature of the process used for extraction of the yew wood, *viz.*, prolonged treatment with boiling water, the possibility could not be entirely excluded that *iso*taxiresinol might also arise from a labile precursor corresponding in structure to lariciresinol. However, no evidence for the existence of an isomer of *iso*taxiresinol has been obtained; extraction of the timber with cold ether yielded, after crystallisation from ethyl acetate, only *iso*taxiresinol, though in smaller quantity than aqueous extraction, doubtless owing to the lower efficiency of the organic solvent.

After removal of *iso*lariciresinol from aqueous extracts of the wood, a highly crystalline optically inactive compound, $C_7H_{14}O_6$, m. p. 237° (yield, 0·04%) was isolated. It formed a penta-acetate, m. p. 200°, and contained one methoxyl group, and when hydrolysed gave *meso*inositol. These properties agree with those of sequoyitol, an inositol methyl ether present in the California redwood (*Sequoia sempervirens*) (Sherrard and Kurth, *J. Amer. Chem. Soc.*, 1929, **51**, 3139) and also in the Western Australian plant *Macrozamia Riedlei* (Riggs, *J.*, 1949, 3199).

Both lignans and inositols are characteristic heartwood constituents of the conifers, and the isolation of *iso*taxiresinol and of sequoyitol from the yew is of particular significance in view of the relation of the *Taxaceæ* to the coniferous trees. Flavone constituents are also widely distributed among the conifers, but compounds of this nature do not appear to occur in the heartwood of the yew. Crude ether and acetone extracts, dissolved in alcoholic hydrochloric acid, gave no characteristic colour with magnesium or zinc, thus indicating the absence of flavanols, flavanones, and flavanolones (3-hydroxy-flavanones) (Pew, *J. Amer. Chem. Soc.*, 1948, **70**, 3031).

Experimental

iso*Taxiresinol* (III; R = H).—(*a*) The heartwood used in this investigation was taken from a fully grown tree of maximum girth nearly 8 feet. Fine shavings of the timber (1000 g.) were covered with water which was boiled for 2 hours, and 3 successive extractions were thus

made, each extract being decanted and concentrated to approx. 300 c.c. After cooling and separation from the dark brown resinous precipitate (A), the aqueous solution was extracted with ether (7 × 150 c.c.). The combined ethereal solutions were dried ($MgSO_4$) and evaporated, leaving a yellow solid. This was refluxed with ethyl acetate (15 c.c.) for 10 minutes during which the mass thickened with the formation of crystalline solid. After cooling overnight, the mixture was filtered and the solid washed thoroughly with cold ethyl acetate. Most of the colour was thereby removed, the product being obtained as faintly pink, very small rods (7·7 g.), m. p. 166—169°. It was once again refluxed with ethyl acetate (15 c.c.) and, when collected (yield, 5·8 g.; m. p. 170°) and recrystallised from 2N-aqueous acetic acid, *iso*taxiresinol was obtained as almost colourless, flat rods (5·4 g.), m. p. 171° (Found: C, 65·9; H, 6·7; OMe, 9·0; active H, 1·33. $C_{19}H_{22}O_9$ requires C, 65·8; H, 6·4; OMe, 9·0; 5 active H, 1·4%). A further quantity of *iso*taxiresinol was obtained from the resinous by-product (A) which partly crystallised after several days. On addition of 40% aqueous acetic acid, the crystalline *iso*taxiresinol remained undissolved, and was collected and recrystallised from 2N-aqueous acetic acid (yield, 3 g.; m. p. 170°). *iso*Taxiresinol dissolved readily in methanol or ethanol, its solutions giving a green ferric reaction. It was moderately soluble in hot water, ether, chloroform and ethyl acetate, and sparingly soluble in benzene.

(*b*) The comminuted heartwood (200 g.) was covered with ether and left for 2 days at room temperature. The resulting solution was decanted, and the oil left on evaporation was refluxed with light petroleum. The petroleum-insoluble residue was dissolved in a small volume of hot ethyl acetate, which was filtered and set aside. A crystalline solid slowly separated and was collected after several weeks. The product (0·4 g.) had m. p. 169°, undepressed on admixture with an authentic sample of *iso*taxiresinol.

iso*Taxiresinol Trimethyl Ether* (iso*Lariciresinol Dimethyl Ether*) (III; R = Me).—Methyl sulphate (2 c.c.) was added in 2 portions during 10 minutes to a solution of *iso*taxiresinol (0·68 g.) in 2N-aqueous sodium hydroxide (12 c.c.) kept at 60°. After being heated on a steam-bath for 10 minutes the white solid (0·7 g.) was collected, dried, and recrystallised from ethyl acetate. *iso*Taxiresinol trimethyl ether separated as very small needles, m. p. 167—168°, undepressed on admixture with *iso*lariciresinol dimethyl ether. *iso*Taxiresinol trimethyl ether was also prepared by methylating taxiresinol in acetone solution with methyl iodide and potassium carbonate (yield 80%) (Found: C, 68·4; H, 7·7; OMe, 32·8. Calc. for $C_{22}H_{28}O_9$: C, 68·0; H, 7·3; 4OMe, 32·0%), $[\alpha]_D^{18}$ +19° in chloroform. Haworth and Kelly (*loc. cit.*) record for *iso*lariciresinol dimethyl ether $[\alpha]_D^{14}$ +20° in chloroform.

iso*Taxiresinol Triethyl Ether* (III; R = Et).—A solution of *iso*taxiresinol (1 g.) in ethyl iodide (5 c.c.) and acetone (20 c.c.) was refluxed with anhydrous potassium carbonate (2 g.) for 30 hours. The product solidified on removal of the solvent and addition of water, and was collected and recrystallised successively from ethanol and ethyl acetate. iso*Taxiresinol triethyl ether* (0·75 g.) separated in needles, m. p. 140° (Found: C, 69·6; H, 8·0. $C_{25}H_{34}O_6$ requires C, 69·7; H, 8·0%).

*Anhydro*iso*taxiresinol Trimethyl Ether.*—*iso*Taxiresinol trimethyl ether (0·2 g.) was heated with potassium hydrogen sulphate (0·8 g.) at 180—190° for ½ hour. The solid which separated on addition of water was collected and recrystallised from methanol, anhydro*iso*taxiresinol trimethyl ether separating as colourless needles, m. p. 149·5°, alone or mixed with anhydro-*iso*lariciresinol dimethyl ether (Found: C, 71·7; H, 7·1. Calc. for $C_{22}H_{26}O_5$: C, 71·4; H, 7·1%).

*Anhydro*iso*taxiresinol Triethyl Ether.*—*Anhydro*iso*taxiresinol triethyl ether*, prepared in the same manner as the anhydro-trimethyl ether, separated from aqueous methanol in needles, m. p. 122·5—123° (Found: C, 72·3; H, 7·8. $C_{25}H_{32}O_5$ requires C, 72·8; H, 7·8%).

iso*Taxiresinol Triethyl Ether Diacetate.*—*iso*Taxiresinol triethyl ether (0·1 g.), anhydrous pyridine (2 c.c.), and acetic anhydride (1 c.c.) were mixed and kept at room temperature for 15 hours. After the mixture had been poured on crushed ice and set aside, the solid was collected and recrystallised from aqueous methanol. iso*Taxiresinol triethyl ether diacetate* separated in very small needles, m. p. 89·5° (Found: C, 68·1; H, 7·3. $C_{29}H_{38}O_8$ requires C, 67·8; H, 7·4).

iso*Taxiresinol Triethyl Ether Dibenzoate.*—*iso*Taxiresinol triethyl ether (0·07 g.), benzoyl chloride (0·3 c.c.), and pyridine (0·5 c.c.) were mixed and left overnight at room temperature. Water was added, and the oily solid separated by decantation was suspended in dilute aqueous ammonia for 10 minutes. When collected and washed with water, dilute hydrochloric acid and again with water, the product was dissolved in boiling alcohol. From the concentrated alcoholic solution crystals of the *dibenzoate* separated which when recrystallised from methanol

formed needles, m. p. (after drying at 100°) 125° (Found : C, 73·0; H, 6·2. $C_{39}H_{42}O_8$ requires C, 73·3; H, 6·6%).

Oxidation of iso*Taxiresinol Triethyl Ether.*—(a) *With concentrated nitric acid.* *iso*Taxiresinol triethyl ether (0·3 g.) and nitric acid (6 c.c.; *d* 1·42) were heated on a steam-bath for ½ hour; afterwards the solution was concentrated to 1 c.c., diluted with water (15 c.c.), and extracted with ether (3 × 20 c.c.). The ethereal solution was washed repeatedly with 2N-sodium carbonate until the alkaline extracts were colourless; it was then washed with water and dried. Evaporation of the ethereal solution gave a crystalline residue which was extracted several times with boiling light petroleum. The solid deposited from the petroleum extracts was recrystallised from alcohol, and separated as pale yellow plates, m. p. 110°, alone or mixed with 1 : 2-diethoxy-4 : 5-dinitrobenzene. Similarly *iso*taxiresinol trimethyl ether (0·2 g.) gave 4 : 5-dinitroveratrole (0·04 g.), m. p. and mixed m. p. 130°.

(b) *With potassium permanganate.* Powdered potassium permanganate (1·5 g.) was added during 2 hours to a refluxing solution of *iso*taxiresinol triethyl ether (0·35 g.) in acetone (40 c.c.). The solution was then concentrated to about 10 c.c., water (10 c.c.) was added, and refluxing continued until reduction of the permanganate was complete (10 minutes). Excess of water was then added, the manganese dioxide was removed by filtration, and the remaining acetone distilled from the straw-coloured filtrate, which when cooled was extracted with ether (3 × 20 c.c.). The ethereal extract was washed with 2N-sodium carbonate (2·0 c.c.) which was then added to the aqueous solution. Acidification of the latter with hydrochloric acid gave a cream-coloured precipitate which when recrystallised from aqueous methanol formed prisms, m. p. 173°, subsequently identified as 2-(3 : 4-*diethoxybenzoyl*)-4-*ethoxy*-5-*methoxybenzoic acid* (IV; R = CO_2H) and obtained colourless (m. p. 173·5°) when further crystallised from benzene–light petroleum (Found : C, 64·5; H, 6·0. $C_{21}H_{24}O_7$ requires C, 64·9; H, 6·2%). An excess of ethereal diazomethane and a solution of the acid in methanol gave the *methyl* ester (IV; R = CO_2Me) which separated from light petroleum in irregular plates, m. p. 111° (Found : C, 65·5; H, 6·3. $C_{22}H_{26}O_7$ requires C, 65·6; H, 6·5%). The acid gave a deep red colour with concentrated sulphuric acid and, when the solution was heated on a steam-bath, 3 : 6 : 7-triethoxy-2-methoxyanthraquinone separated as long yellow needles. The oxidation of *iso*-taxiresinol trimethyl ether (0·22 g.) under similar conditions gave veratroylveratric acid (0·04 g.), m. p. 221° (lit., 221—222°), and its methyl ester, m. p. 159° (lit., 161°).

(c) *With potassium dichromate.* A mixture of *iso*taxiresinol triethyl ether (0·55 g.), potassium dichromate (2·5 g.), and glacial acetic acid (15 c.c.) was heated under reflux for 3 hours. After addition of water (100 c.c.) the mixture was extracted with ether (3 × 60 c.c.), and the washed ethereal solution extracted with 2N-sodium hydroxide. A yellow solid was precipitated on acidification of the alkaline extract and this was collected and recrystallised successively from aqueous ethanol and benzene, thus affording the acid (IV; R = CO_2H) in colourless prisms, m. p. 173° (Found : C, 64·9; H, 6·3%). Similarly, from the trimethyl ether veratroylveratric acid, m. p. 220—221°, was obtained.

3 : 4-*Diethoxybenzaldehyde.*—Ethyl sulphate (38·5 g.) and a solution of potassium hydroxide (18·4 g.) in water (50 c.c.) were added slowly and with stirring during 10 minutes to 3 : 4-dihydroxybenzaldehyde (13·8 g.), the reaction mixture being heated on a steam-bath. After being heated and stirred for a further 10 minutes the mixture was cooled and the oily layer extracted with ether. The washed and dried ethereal solution on distillation gave 3 : 4-diethoxybenzaldehyde as a pale yellow oil (15·4 g., 79%), b. p. 280—282° (lit., 278—280°). 3 : 4-*Diethoxybenzaldehyde semicarbazone* separated from alcohol in faintly yellow needles, m. p. 175° (Found : C, 57·2; H, 6·9. $C_{12}H_{17}O_3N_3$ requires C, 57·3; H, 6·8%).

3 : 4-*Diethoxybenzoic Acid.*—3 : 4-Diethoxybenzaldehyde (33 g.) was added to a solution of potassium permanganate (43 g.) in water (800 c.c.), and the mixture boiled for 5 minutes to complete the oxidation. Acidification of the mixture with a stream of sulphur dioxide precipitated 3 : 4-diethoxybenzoic acid in needles, m. p. 165° (31·5 g., 88%), raised by recrystallisation from benzene–light petroleum or alcohol–water to 166—167° (lit., 165—166°) (Found : C, 62·5; H, 6·7. Calc. for $C_{11}H_{14}O_4$: C, 62·8; H, 6·7%). 3 : 4-*Diethoxybenzamide* was prepared by treating the acid successively with thionyl chloride and concentrated aqueous ammonia; it separated from methanol in needles, m. p. 183·5° (Found : C, 63·5; H, 7·1; N, 6·4. $C_{11}H_{15}O_3N$ requires C, 63·1; H, 7·2; N, 6·7%).

5 : 3′ : 4′-*Triethoxy*-4-*methoxy*-2-*methylbenzophenone* (IV; R = Me).—*O*-Ethylvanillin (25 g.) and amalgamated zinc (130 g.) were refluxed with concentrated hydrochloric acid (260 c.c.) for 20 hours; excess of zinc was then removed and the mixture steam-distilled. 4-Ethoxy-3-methoxytoluene, isolated from the distillate with ether, was thus obtained as a colourless

oil (9·3 g., 40%), b. p. 227—228° (lit., b. p. 223—224°). 3 : 4-Diethoxybenzoyl chloride was prepared from the acid and thionyl chloride, and separated from light petroleum in colourless needles.

Powdered aluminium chloride (11·1 g.) was added during 10 minutes to a solution of 4-ethoxy-3-methoxytoluene (5·45 g.) and 3 : 4-diethoxybenzoyl chloride (7·5 g.) in nitrobenzene (30 g.), the mixture being cooled in an ice-bath. After being left overnight at room temperature the solution was poured into a mixture of concentrated hydrochloric acid (10 c.c.) and crushed ice. The nitrobenzene was removed by steam-distillation and the residual oil isolated with chloroform. After washing of the extract with dilute sodium hydroxide and water, the solvent was evaporated and the oily residue dissolved in a small volume of boiling methanol. 5 : 3′ : 4′-*Triethoxy*-4-*methoxy*-3-*methylbenzophenone* (4·7 g., 40%) separated on cooling and when crystallised from methanol formed colourless prisms, m. p. 115° (Found : C, 70·2; H, 7·0. $C_{21}H_{26}O_5$ requires C, 70·4; H, 7·3%).

2-(4-*Ethoxy*-3-*methoxyphenyl*)*ethylamine*.—Ethyl sulphate (49 c.c.), and a solution of potassium hydroxide (27·6 g.) in water (60 c.c.), were added with vigorous agitation during 10 minutes to vanillin (45·6 g.) melted on a steam-bath. After a further 10 minutes' heating, the mixture was cooled and placed in a refrigerator for 3 hours. The light brown crystalline mass of *O*-ethylvanillin was ground in a mortar with a small volume of water, collected, and air-dried at 40°; the yield was 49·5 g. (90%) and the m. p. 61° (lit., 64°).

Ethylvanillin (25 g.) and malonic acid (35 g.), dissolved in pyridine (50 c.c.) and piperidine (2·5 c.c.), were heated on a steam-bath for 1 hour. After refluxing for a further 15 minutes the mixture was diluted with water, acidified with hydrochloric acid, and cooled. The precipitated 4-ethoxy-3-methoxycinnamic acid, m. p. 203° (lit., 205°), was collected and dissolved in a small volume of N-sodium hydroxide. Sodium amalgam (700 g.; 3%) was gradually added during 2½ hours with mechanical stirring and occasional additions of concentrated hydrochloric acid. The solution was decanted, treated with charcoal, filtered, and acidified, thus liberating β-(4-ethoxy-3-methoxyphenyl)propionic acid (28 g.), m. p. 130° (lit., 130°). This acid was dissolved in methanolic hydrogen chloride (150 c.c.) and refluxed for 15 hours; after removal of the solvent *in vacuo*, sodium hydrogen carbonate solution was added and the crystalline residue (27 g.) dissolved in boiling light petroleum. *Methyl* β-(4-*ethoxy*-3-*methoxyphenyl*)*propionate* separated in prisms, m. p. 37—38° (Found : C, 65·3; H, 8·0. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%).

The methyl ester (26 g.) was added during 5 minutes to hot 90% aqueous hydrazine hydrate. Heating was continued for 3 hours on a steam-bath and the crystalline hydrazide precipitated with water (50 c.c.). The *hydrazide* separated from benzene in prisms, m. p. 123° (Found : C, 60·2; H, 7·5; N, 11·9. $C_{12}H_{18}O_3N_2$ requires C, 60·5; H, 7·6; N, 11·8%). A solution of the hydrazide in 10% hydrochloric acid (150 c.c.) was covered with ether and cooled in ice, and sodium nitrite added slowly until present in excess. The dried ($CaCl_2$) ethereal solution was added to ethanol (50 c.c.), and the ether expelled by warming, the solution then being refluxed for 2 hours. A solution of sodium hydroxide (8·0 g.) in water (20 c.c.) was added, and after a further 15 hours' refluxing, most of the alcohol was evaporated. Water was then added and the base extracted with ether, distillation of the extract giving 2-(4-ethoxy-3-methoxyphenyl)ethylamine (5·7 g.) as an oil, b. p. 172—174°/15 mm. (lit., 165°/15 mm.). The picrate, prepared from sodium picrate and a solution of the amine in 20% aqueous lactic acid, separated from alcohol in orange-red prisms, m. p. 183° (lit., 181—182°) (Found : C, 48·3; H, 4·7; N, 13·1. Calc. for $C_{17}H_{20}O_9N_4$: C, 48·1; H, 4·7; N, 13·2).

3 : 4-*Diethoxy*-N-[2-(4-*ethoxy*-3-*methoxyphenyl*)*ethyl*]*benzamide*.—3 : 4-Diethoxybenzoyl chloride (5·2 g.) dissolved in benzene (25 c.c.) was gradually added to a solution of 2-(4-ethoxy-3-methoxyphenyl)ethylamine (4 g.) in pyridine (10 c.c.). After 15 minutes' heating on a steam-bath, most of the benzene was distilled, excess of chloroform was added, and the solution washed with 10% hydrochloric acid and with water. The chloroform was then evaporated, and the crystalline residue recrystallised from methanol. The *amide* (6·85 g., 86%) separated in needles, m. p. 148·5° (Found : C, 68·5; H, 7·7; N, 3·7. $C_{22}H_{29}O_5N$ requires C, 68·2; H, 7·5; N, 3·6%).

1-(3′ : 4′-*Diethoxyphenyl*)-7-*ethoxy*-3 : 4-*dihydro*-6-*methoxy*isoquinoline (V).—A solution of the above amide (7·5 g.) in toluene (30 c.c.) was refluxed with phosphorus oxychloride (15 g.) for 2 hours. Toluene and excess of phosphorus oxychloride were removed *in vacuo*, and the residual gum was dissolved in boiling 10% hydrochloric acid (70 c.c.). The amine hydrochloride which separated on cooling crystallised from acetone in small yellow needles, m. p. 123°. A solution of the hydrochloride in chloroform (350 c.c.) was shaken with 2N-aqueous sodium carbonate

(2 × 50 c.c.), and then washed, dried ($MgSO_4$), and evaporated. The oily residue dissolved in a small volume of boiling benzene and treated with excess of light petroleum gave 1-(3 : 4-*diethoxyphenyl*)-7-*ethoxy*-3 : 4-*dihydro*-6-*methoxy*isoquinoline (5·9 g., 82%), m. p. 113—114°, which when recrystallised from benzene–light petroleum formed faintly brown, rectangular prisms, m. p. 115—115·5° (Found : C, 71·5; H, 7·4. $C_{22}H_{27}O_4N$ requires C, 71·5; H, 7·4%).

A solution of the dihydro*iso*quinoline (4·3 g.) in methyl iodide (20 c.c.) was refluxed for 20 minutes and, after removal of the excess of iodide, the crystalline residue was dissolved in boiling *iso*propyl alcohol (20 c.c.). The bright yellow *methiodide* (5·9 g.), m. p. 191·5°, which separated was recrystallised from water, thus being obtained as yellow needles, m. p. 192° (Found, in a specimen dried at 100° *in vacuo* : C, 53·4; H, 6·1. $C_{23}H_{30}O_4NI,\frac{1}{2}H_2O$ requires C, 53·1; H, 6·0%).

2-[2-(3 : 4-*Diethoxybenzoyl*)-4-*ethoxy*-5-*methoxyphenyl*]*ethyltrimethyl Ammonium Iodide* (VI).—A solution of the dihydro*iso*quinoline methiodide (2 g.) in methyl iodide (12 c.c.) was shaken vigorously at room temperature with N-aqueous sodium hydroxide (80 c.c.) for 1½ hours. The methyl iodide layer was removed, the aqueous solution extracted 3 times with chloroform, and the methyl iodide and chloroform solutions were combined and dried ($MgSO_4$). The yellow gum which remained on removal of the solvent was dissolved in boiling benzene (15 c.c.) and, on addition of petroleum, a cream-coloured precipitate separated (2·1 g., 96%). Recrystallised from benzene–light petroleum, 2-[2-(3 : 4-*diethoxybenzoyl*)-4-*ethoxy*-5-*methoxyphenyl*]*ethyltrimethylammonium iodide* separated in colourless needles, m. p. 159° (Found : C, 53·9; H, 6·6; N, 3·1. $C_{25}H_{36}O_5NI$ requires C, 53·8; H, 6·5; N, 2·5%). The iodide was soluble in warm water, its solution giving a precipitate of silver iodide with silver nitrate in dilute nitric acid. The quaternary *picrate*, prepared by addition of aqueous sodium picrate to a solution of the iodide in 5% lactic acid, separated from benzene in yellow rectangular prisms, m. p. 171·5° (Found : C, 56·7; H, 5·6. $C_{31}H_{38}O_{12}N_4$ requires C, 56·5; H, 5·8%).

5 : 3′ : 4′-*Triethoxy*-4-*methoxy*-2-*vinylbenzophenone* (IV; R = $CH{:}CH_2$).—The iodide (VI) (1·8 g.), suspended in 2N-aqueous hydroxide (50 c.c.), was heated on a steam-bath for 15 minutes, whereupon trimethylamine was evolved and a yellow oil separated which solidified on cooling. This was collected and extracted 3 times with large volumes of light petroleum. The petroleum-insoluble residue, recrystallised from benzene–light petroleum, gave a small quantity of the unchanged iodide, m. p. 158—159°. The combined petroleum extracts were concentrated and deposited a crystalline mass of the *vinyl* compound (IV; R = $CH{:}CH_2$), which separated from light petroleum and from methanol in prisms (0·67 g., 56%), m. p. 118—118·5° (Found : C, 71·5; H, 7·0. $C_{22}H_{26}O_5$ requires C, 71·3; H, 7·1%).

2-(3 : 4-*Diethoxybenzoyl*)-4-*ethoxy*-5-*methoxybenzoic Acid* (IV; R = CO_2H).—(*a*) Finely powdered potassium permanganate (0·85 g.) was added gradually during 10 minutes to a solution of the vinyl compound (IV; R = $CH{:}CH_2$) (0·4 g.) in boiling acetone (60 c.c.). Refluxing was continued for 45 minutes, water (100 c.c.) was added, and most of the acetone evaporated. Manganese dioxide was removed by filtration, and the almost colourless filtrate concentrated to 50 c.c. and acidified with hydrochloric acid. The precipitated solid was collected and shaken with cold 2N-sodium carbonate, and the solution filtered from a small quantity of non-acidic material and acidified. The resulting product crystallised from aqueous methanol (0·25 g.) in colourless prisms, m. p. 173°, and recrystallisation from benzene–light petroleum gave 2-(3 : 4-diethoxybenzoyl)-4-ethoxy-5-methoxybenzoic acid as prisms, m. p. 173·5° undepressed by the acid obtained from the oxidation of *iso*taxiresinol triethyl ether (Found : C, 64·8; H, 6·2. Calc. for $C_{21}H_{24}O_7$: C, 64·9; H, 6·2%). The methyl ester, prepared by addition of excess of ethereal diazomethane to a solution of the acid in methanol, separated from light petroleum in irregular plates, m. p. 111—111·5° alone or mixed with the methyl ester of the acid derived from the natural product (Found : C, 65·9; H, 6·3. Calc. for $C_{22}H_{26}O_7$: C, 65·6; H, 6·5%). Sulphuric acid (5 drops of 89%) was added to the synthetic acid (25 mg.), and the deep red solution thus formed heated on a steam-bath for 5 minutes, by which time a mass of yellow needles separated. The mixture was diluted with water, and the yellow solid collected, washed well with acetone and recrystallised from acetic acid. 3 : 6 : 7-*Triethoxy*-2-*methoxyanthraquinone* separated in bright yellow needles, m. p. 225° (Found : C, 68·5; H, 6·2. $C_{21}H_{22}O_6$ requires C, 68·1; H, 6·0%).

(*b*) A solution of 5 : 3′ : 4′-triethoxy-4-methoxy-2-methylbenzophenone (1·0 g.) in acetic acid (30 c.c.) and water (7·5 c.c.) was refluxed with potassium dichromate (4 g.) for 3 hours. The solution was then poured into water (200 c.c.) and extracted with ether (2 × 100 c.c.). The ethereal and aqueous layers were filtered from a yellow insoluble solid (0·08 g.) which, when recrystallised from acetic acid, separated in bright yellow needles, m. p. 225°, undepressed

on admixture with 3 : 6 : 7-triethoxy-2-methoxyanthraquinone. The ethereal solution, after being washed with water (3 × 50 c.c.), was extracted with 2N-sodium carbonate (2 × 15 c.c.). Acidification of the alkaline solution precipitated a solid (0·2 g.), m. p. *ca.* 142°, which after further purification through 2N-sodium carbonate and crystallisation from aqueous methanol and benzene–light petroleun, separated in colourless prisms, m. p. 172—173°, undepressed on admixture with the acid (IV; R = CO_2H) (Found: C, 64·6; H, 6·2%). The acid gave a deep red colour with concentrated sulphuric acid and, when the solution was warmed, yellow needles of the triethoxymethoxyanthraquinone were formed. The methyl ester, prepared by the action of diazomethane, crystallised as irregular plates, m. p. and mixed m. p. 111°.

The sodium carbonate-washed ethereal solution, washed with water and evaporated, gave on crystallisation from methanol pale yellow needles (0·3 g.), m. p. 152°. This compound was not further examined.

Sequoyitol.—The yew heartwood (1200 g.) was extracted twice with cold light petroleum and twice with ether. It was then dried and steeped in cold water for 2 days, the solution then decanted, and the wood once again treated with cold water. The combined aqueous extracts were concentrated to about 150 c.c. and set aside for a day during which the brown tarry precipitate crystallised. Treatment of the solid with 40% aqueous acetic acid gave *iso*taxiresinol (2·5 g.), m. p. 170°, a further quantity being obtained by extracting the aqueous solution with ethyl acetate. The clear orange aqueous liquid was then concentrated *in vacuo* and the residual gum refluxed several times with large volumes of methanol. The combined filtered extracts were concentrated to 50 c.c. and left for 3 days, whereupon a crystalline solid separated which was collected and recrystallised from methanol. Sequoyitol (0·51 g.) was thus obtained as colourless rectangular prisms, m. p. 237° (Found: C, 42·9; H, 7·5; OMe, 15·7. Calc. for $C_7H_{14}O_6$: C, 43·3; H, 7·3; 1OMe, 16·0%). The compound (0·05 g.) was demethylated by refluxing it with hydriodic acid (1·0 c.c.; *d* 1·7) for 1 hour. The product separated from aqueous ethanol in colourless prisms, m. p. 221°, alone or mixed with authentic *meso*inositol. The acetate had m. p. 215° alone or mixed with *meso*inositol hexa-acetate.

Sequoyitol Penta-acetate.—The cyclitol (0·1 g.), fused sodium acetate (0·2 g.), and acetic anhydride (5 c.c.) were heated on a steam-bath for 2 hours. Excess of water was added and the mixture warmed to destroy excess of anhydride. The solvent was then removed *in vacuo*, and the addition of water gave sequoyitol penta-acetate (0·18 g.) which, when recrystallised successively from benzene–light petroleum and alcohol, separated as colourless needles, m. p. 200° (Found: C, 50·4; H, 5·7; OMe, 8·5; OAc, 49·4. Calc. for $C_{17}H_{24}O_{11}$: C, 50·5; H, 6·0; 1OMe, 7·8; 5OAc, 53·2%).

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