The Position of the Biphenyl Linkage in the Ergot Pigments. A Partial Synthesis of Ergoflavin

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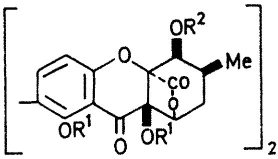
Summary The ergot pigments, ergochrysin A, the secalonic acids A, B, C, and D, and ergoxanthin have 2,2′-linkages between the biphenyl residues.

THE pigment, ergoflavin (1; $R^1 = R^2 = H$), of ergot has[1,2] a 2,2′-linkage between the two "halves." The position of this linkage in the associated ergochrysin A, and its transformation product, isoergochrysin A, has been provisionally assigned,[3] as in (2) and (3), respectively. A 4,4′-junction between the two moieties of the cognate secalonic acids, A, B, C, and D [stereochemical variants of (4)] has been tentatively suggested.[3–7] We report a definitive resolution of these ambiguities.

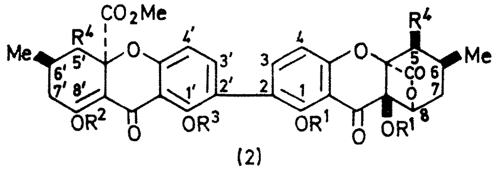
Thus methylation (diazomethane) of ergochrysin A gave 1,8′,9-tri-*O*-methylergochrysin A (2; $R^1 = R^2 =$ Me, $R^3 =$ H, $R^4 =$ H, OH) which was further methylated (dimethyl sulphate–acetone–potassium carbonate) to 1,1′,8′,9-tetra-*O*-methylergochrysin A (2; $R^1 = R^2 = R^3 =$ Me, $R^4 =$ H, OH). The enolic methoxy-group of this tetra-*O*-methyl ether was removed and the resultant 1,1′,9-tri-*O*-methylergochrysin A (2; $R^1 = R^3 =$ Me, $R^2 =$ H, $R^4 =$ H, OH) oxidised (Jones' reagent) to 1,1′,9-tri-*O*-methylergochrysinone A (2; $R^1 = R^3 =$ Me, $R^2 =$ H, $R^4 =$ O). Alkaline degradation of this formed 3,3′-diacetyl-4,4′-dihydroxy-2,2′-dimethoxybiphenyl[2] (5; $R^1 =$ Me, $R^2 =$ H). The di-*O*-ethyl ether (5; $R^1 =$ Me, $R^2 =$ Et) was identical with that of definitive structure[2] from ergoflavin. Similarly 3,3′-diacetyl-2′,4-diethoxy-2,4′-dimethoxybiphenyl was obtained from isoergochrysin A and also from a "crossed" Ullmann condensation between 6-ethoxy-3-iodo-2-methoxyacetophenone (6; $R^1 =$ Et, $R^2 =$ Me, $R^3 =$ I) and 2-ethoxy-3-iodo-6-methoxyacetophenone (6; $R^1 =$ Me, $R^2 =$ Et, $R^3 =$ I). Hence, ergochrysin A has a 2,2′- and isoergochrysin A (3) a 2,4′-linkage.

Similarly, the biphenyl (5; $R^1 =$ Me, $R^2 =$ Et) was obtained from secalonic acid D[6] which (together with its optical antipode,[6] secalonic acid A) must also have 2,2′-linkages as in (4).

Our extensive n.m.r. data for various methylated ergot pigments and for analogous biphenyls show clearly that methoxy-groups *ortho* to the biphenyl linkage give rise to signals at *ca.* τ 6·5, whilst for *para*-methoxy-groups the signals are at *ca.* τ 6·1 (*cf.* similar observations[8]). On this basis our 1,1'-di-*O*-methylsecalonic acids A and C (and hence secalonic acids A and C) and the cognate ergoxanthin (7),[9] have 2,2'-linkages. Our work also shows that the n.m.r. signals of the C-3, C-4, C-3', and C-4' protons are diagnostic of the nature of the biphenyl ring junction and establish that secalonic acid B also has a 2,2'-linkage. Thus all the known ergot pigments belong to this 2,2'-series.



(1)



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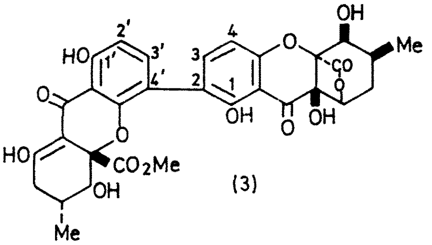

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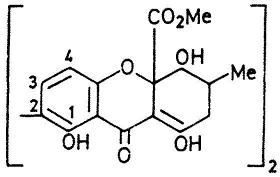

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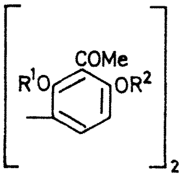

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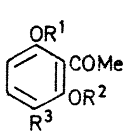

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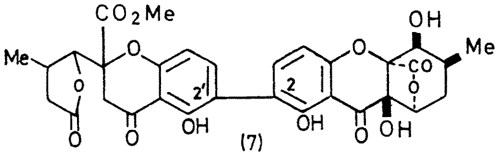
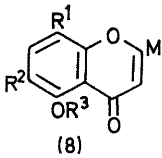


(7)

Synthetic (5; $R^1 = Me$, $R^2 = Et$) was obtained by Ullmann coupling of (6; $R^1 = Et$, $R^2 = Me$, $R^3 = I$) which was prepared from 6-ethoxy-2-hydroxyacetophenone (6; $R^1 = Et$, $R^2 = R^3 = H$) by successive iodination and methylation. Likewise, (5; $R^1 = Et$, $R^2 = Me$) was obtained (a) from tetra-*O*-ethylergoflavinone and (b) from Ullmann coupling of (6; $R^1 = Me$, $R^2 = Et$, $R^3 = I$) which was prepared by successive iodination and ethylation of 2-hydroxy-6-methoxyacetophenone (6; $R^1 = Me$, $R^2 = R^3 = H$). It follows that iodination of acetophenones of type (6; $R^1 = Me$; $R^2 = R^3 = H$) proceeds *ortho* to the hydroxy-group and not *para* as claimed.[10] Hence many cognate derivatives[10] are incorrectly formulated.



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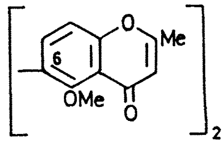

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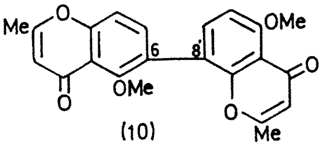

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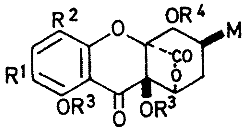

(11)

Likewise, 5-hydroxy-2-methylchromone (8; $R^1 = R^2 = R^3 = H$) yields the 6-iodo-2-methylchromone (8; $R^1 = R^3 = H$, $R^2 = I$) and not the 8-iodo-derivative (8; $R^1 = I$ $R^2 = R^3 = H$).[4,10] Coupling of (8; $R^1 = H$, $R^2 = I$, $R^3 = Me$) formed the 6,6'-bichromonyl (9) (*cf.* Franck[4,5]), which gave (5; $R^1 = Me$, $R^2 = H$)[3] on alkaline degradation. Wesseley–Moser rearrangement of (9), gave, after remethylation of the product, 6,8'-bichromonyl (10) and not the corresponding 8,8'-bichromonyl,[4,5] since alkaline degradation of (10), followed by ethylation formed 3,3'-diacetyl-2',4-diethoxy-2,4'-dimethoxybiphenyl.

Iodination of hemiergoflavin (11; $R^1 = R^2 = R^3 = R^4 = H$) does not yield (11; $R^1 = R^3 = R^4 = H$, $R^2 = I$),[2] but the 6-iodo-derivative (10; $R^1 = I$, $R^2 = R^3 = R^4 = H$) since Ullmann coupling of (10; $R^1 = I$, $R^2 = H$, $R^3 = Me$, $R^4 = PhCO$) gave 5,5'-di-*O*-benzoyl-1,1',9,9'-tetra-*O*-methylergoflavin (1; $R^1 = Me$, $R^2 = PhCO$) which formed ergoflavin (1; $R^1 = R^2 = H$) with hydriodic acid.

All new compounds had the appropriate spectral and analytical characteristics.

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