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BIOGENETIC MODELS FOR THE FORMATION OF NATURAL CINNAMYLPHENOLS AND NEOFLAVANOIDS

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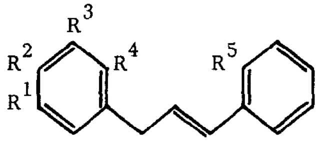
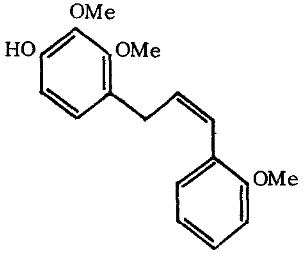
The cinnamylphenols have recently been recognised[1] as a new group of natural products which co-occur[1,2] with neoflavanoids in a number of Dalbergia and Machaerium species. These observations led to biogenetic proposals[3] in which the cinnamylation of phenols (or their polyketide equivalents) could give rise either to the neoflavanoids or to the cinnamylphenols. Nine natural cinnamylphenols are known at present, of which six have trans- and three have cis-stereochemistry. We now report the syntheses of five natural trans-cinnamylphenols, and experiments concerning the mechanism of the acid-catalysed reaction between phenols and cinnamyl alcohols.

The mechanistic feasibility of the biogenetic proposal[3] has recently been demonstrated[4] by the observation that cinnamyl alcohol reacts either with resorcinol or with pyrogallol in aqueous acetic acid giving both 3,3-diarylpropenes (neoflavanoids) and 1,3-diarylpropenes (cinnamylphenols). This reaction type has now been extended to yield the five natural cinnamylphenols (I, III, V,.VI, and VII) from the appropriate phenol and trans-cinnamyl alcohol. It has been found that the use of 50% aqueous formic acid (100^{o}; 1 hr.) suppresses the formation of neoflavanoids and gives trans-cinnamylphenols as the major products. In three reactions, a, b, and e (see Table), mixtures of two products, the o- and the p-cinnamylphenols, were isolated in each case, whereas in the reactions c and d only one cinnamylphenol was isolated in good yield.

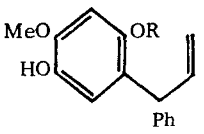
Cinnamyl acetates may also be used in these reactions in place of cinnamyl alcohols, and this is advantageous because the cinnamylphenols are produced in similar yields with a reduction of other products. In connection with the natural occurrence of cis-cinnamylphenols,[1] the acid-catalysed reactions between various phenols and cis-cinnamyl alcohols and their acetates have also been studied, but in no case was a *cis*-cinnamylphenol isolated as a reaction product. The possibility of an acid-catalysed stereomutation of *cis*- to *trans*-cinnamylphenols is most unlikely since it has been shown that mucronulastyrene (with a *cis*-double bond) is not isomerised to the *trans*-isomer under the conditions of the cinnamylation reaction. Thus, reaction of 2, 3, 4-trimethoxyphenol and *o*-acetoxy-*cis*-cinnamyl acetate gave the petrostyrene isomer (IX; 15% yield), 2, 4-dimethoxyphenol and *o*-hydroxy-*cis*-cinnamyl alcohol gave the *trans*-cinnamylphenol (X; 20% yield), and no trace of villostyrene (XI) was obtained from the reaction between 2, 3-dimethoxyphenol and *o*-methoxy-*cis*-cinnamyl alcohol.



		R^1	R^2	R^3	R^4	R^5
(I)	Obtusastyrene	H	OH	H	H	H
(II)		H	H	H	OH	H
(III)	Obtustyrene	H	OH	H	OMe	H
(IV)		H	OMe	H	OH	H
(V)	Violastyrene	OMe	OH	H	OMe	H
(VI)	Isoviolastyrene	OH	OMe	H	OMe	H
(VII)	Mucronustyrene	H	OH	OMe	OMe	H
(VIII)		H	OMe	OMe	OH	H
(IX)		OMe	OMe	OMe	OH	OH
(X)		OH	OMe	H	OMe	OH

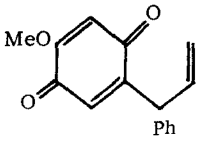


(XI)



(XII) R = H

(XIII) R = Me



(XIV)

TABLE

The reaction of phenols with cinnamyl alcohol in aqueous formic acid

	Phenol	Products*		M.p.	Yield[†]
(a)	Phenol	Obtusastyrene	(I)	(62-63°)	30
			(II)	(68°)[‡]	15
(b)	3-Methoxyphenol	Obtustyrene	(III)	(oil)	25
			(IV)	(70°)	30
(c)	2, 5-Dimethoxyphenol	Violastyrene	(V)	(84°)	60
(d)	2, 4-Dimethoxyphenol	Isoviolastyrene	(VI)	(87°)	65
(e)	2, 3-Dimethoxyphenol	Mucronustyrene	(VII)	(oil)	35
			(VIII)	(oil)	30

[*] Satisfactory spectrometric (i.r., u.v., n.m.r., and mass spectra) and analytical data have been obtained for all new compounds. Direct comparisons have been made between the natural products and synthetic samples where appropriate.

[†] Percentage yields are based upon the amount of product isolated, and no allowance has been made for unreacted phenol (20-40%) generally present in the reaction mixture.

[‡] Lit.,[5] m.p. 55.5-56.5°.

At first sight, these reactions between phenols and *cis*- and *trans*-cinnamyl alcohols (or their acetates) to give *trans*-cinnamylphenols could have involved alkylation by the mesomeric cation $(Ar{-}CH{=}CH{-}CH_2^{+} \longleftrightarrow Ar{-}\overset{+}{C}H{-}CH{=}CH_2)$. The situation is in fact more complex. Thus, neoflavanoids are the major products from the reaction between phenols and (±)-1-phenylallyl alcohol in aqueous propionic acid: 4-hydroxy-2-methoxyphenol and (±)-1-phenylallyl alcohol gave the dalbergiquinol (XII) (with only a trace of cinnamylphenol), and 2, 4-dimethoxyphenol with (±)-1-phenylallyl alcohol gave the dalbergiquinol (XIII; 35% yield) and isoviolastyrene (VI; 30% yield). Aerial oxidation of the dalbergiquinol (XII) gave (±)-4-methoxydalbergione (XIV).[6] An interesting direct oxidation of the dalbergiquinol (XIII) to the dalbergione (XIV) was achieved during purification by thin layer chromatography on silver nitrate impregnated silica gel, using chloroform as the solvent.

These results show that the acid-catalysed reaction of phenols with cinnamyl alcohol and 1-phenylallyl alcohol involves reaction mechanisms having some S_N2 character, since they exclude the possibility that the same mesomeric 1-phenylallyl cation is involved as an intermediate in both cases. Similar results have been reported for a number of substitution reactions of allylic systems.[7]

Since this work was completed, Dr. Jurd has kindly informed us that the acid-catalysed reaction between phenols and cinnamyl alcohol may be successfully achieved in aqueous citric acid solution, and Cardillo, Cricchio, and Merlini[8] have reported the synthesis of other cinnamylphenols using Jurd's original method.[4]

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