Tetrahedron, 1966, Vol. 22, pp. 3491 to 3499. Pergamon Press Ltd. Printed in Northern Ireland

SYNTHESIS OF (±)-LATIFOLIN DIMETHYL ETHER

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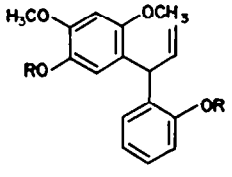
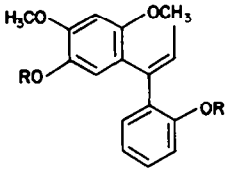
(*Received* 1 *January* 1966; *accepted for publication* 2 *May* 1966)

Abstract—(±)-Latifolin dimethyl ether has been synthesized by coupling 1,2,4-trimethoxybenzene and *o*-methoxycinnamyl cation. The isomeric benzylstyrene is also a product of the reaction. Among the possible biogenetic routes for the related compounds present in *Dalbergia latifolia* the most likely steps seem to be phenylcinnamic esters and 4-phenylcoumarins followed by stages of reduction. The alternative of cinnamyl cation functioning will limit the biosynthesis only to latifolin type of compounds.

LATIFOLIN, the chief constituent of *Dalbergia latifolia* Roxb, the Blackwood or Rosewood of India, possesses a novel γ,γ-diphenylallyl structure (Ia). This assignment[1] was based upon elemental analysis, spectral data, degradation of the methyl ether (Ib) to *o*-methoxybenzoic acid and by direct comparison of the dimethyl ether of isolatifolin (IIa) with that of a synthetic sample. The position of the two free hydroxyl groups although assigned earlier on biogenetic and other grounds, was proved unequivocally by synthesizing the diethyl ether (IIb) of isolatifolin and comparing it with that prepared from latifolin.[2] Further proof was also provided by degradation of Ic through IIb to 2,4-dimethoxy-2',5-diethoxy-benzophenone and comparison with a synthetic sample.[2]



I
a, R=H
b, R=CH_3
c, R=C_2H_5



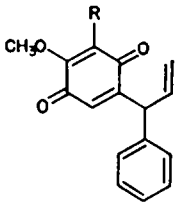
II
a, R=CH_3
b, R=C_2H_5

We now report a synthesis of the racemic dimethyl ether of latifolin. Literature regarding the synthesis of a γ,γ-diphenylpropene skeleton is scanty; Claisen[3] prepared 2-(α-phenylallyl)-phenol by heating phenyl cinnamyl ether. At the commencement of this work there was only a preliminary communication from Eyton *et al.*[4] who used this method for the synthesis of 3-methoxydalbergenone* (IIIa). More recently

* As explained in our earlier paper[1a] the name dalbergenone is preferable to dalbergione for the reason that the compound is ethylenoid and quinonoid. Further it has not got the ring structure of dalbergin and the term dalbergione may suggest that it has. The modified name is free from these defects and is not far different and is not likely to cause confusion. The name is hereafter used, to denote the unsubstituted quinone skeleton only.

[1] S. Balakrishna, M. M. Rao and T. R. Seshadri, *Tetrahedron* **18**, 1503 (1962).
[2] Darshan Kumari, S. K. Mukerjee and T. R. Seshadri, *Tetrahedron* **21**, 1495 (1965).
[3] L. Claisen and E. Tietze, *Ber. Dtsch. Ges.* **58**, 275 (1925).
[4] W. B. Eyton, W. D. Ollis, I. O. Sutherland, L. M. Jackman, O. R. Gottlieb and M. T. Magalhaes, *Proc. Chem. Soc.* 301 (1962).

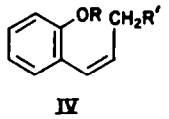
details of the synthesis of 3-methoxydalbergenone and 3,4-dimethoxydalbergenone (IIIb) have been reported.[5] Another possible approach is the construction of a diphenylallyl system from α,α-diphenylethylene.[6]



III
a, R=H
b, R=OCH3

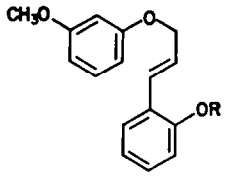
In our initial attempt to utilize Claisen migration as the key step to the latifolin skeleton we required 3-methoxyphenyl-2-methoxycinnamyl ether (Va) as the intermediate. The necessary *o*-hydroxycinnamyl alcohol (IVa) was prepared by the reduction of coumarin with LAH using a modification of the Karrer procedure.[7] Methylation of IVa gave the methoxy alcohol (IVb) as a liquid which has the required UV spectrum and was characterized by the preparation of a 3,5-dinitrobenzoate. White and Fife[8] reported some difficulty in preparing the bromides of *p*- and *m*-methoxycinnamyl alcohols using hydrogen bromide because of their tendency to undergo acid catalysed polymerization. No such difficulty was observed in the case of *o*-methoxycinnamyl alcohol which was converted into the chloride (IVc) using thionyl chloride and catalytic amounts of pyridine. Attempted purification of it by distillation resulted in total destruction. The chloride, however, had the expected spectral and other properties but it failed to react satisfactorily with resorcinol monomethyl ether. Although a number of modifications were adopted only a poor yield of impure ether could be obtained. In an alternative route to the ether (Va) *o*-tosyloxycinnamyl bromide[9] gave with monomethylresorcinol, 3-methoxyphenyl-2'-tosyloxycinnamyl ether (Vb) in excellent yield. Mild alkaline hydrolysis gave the phenol ether (Vc) which was not characterized but directly methylated to the methyl ether (Va). The product was a brownish gum which after chromatography was obtained crystalline and had the expected properties. It however failed to undergo Claisen migration. Heating at 220° under reduced pressure or in refluxing diethylaniline or decalin did not give any alkali soluble product. The alkali insoluble part from these attempts was essentially the recovered ether as shown by TLC. The tosyloxy cinnamyl ether (IVb) also failed to undergo Claisen migration when heated to about 190°; higher temperature caused charring. This suggests that the electromeric effect is not the only one involved. The factors responsible are currently under investigation and will be the matter of a forthcoming publication. This route was therefore abandoned.

[5] M. F. Barnes, W. D. Ollis, I. O. Sutherland, O. R. Gottlieb and M. T. Magalhaes, *Tetrahedron* **21**, 2707 (1965).
[6] C. Walling and L. Bollyky, *J. Org. Chem.* **29**, 2699 (1964).
[7] P. Karrer and P. Bannerjea, *Helv. Chim. Acta* **32**, 1692 (1949).
[8] W. N. White and W. K. Fife, *J. Amer. Chem. Soc.* **83**, 3852 (1961).
[9] Darshan Kumari, S. K. Mukerjee and T. R. Seshadri, unpublished work.



IV

a, R = H; R′ = OH
b, R = CH_3; R′ = OH
c, R = CH_3; R′ = Cl



V

a, R = CH_3
b, R = Tosyl
c, R = H

An attempt to build a vinyl residue on 2,4,5,2′-tetramethoxybenzophenone failed as the ylide from triphenyl methoxymethyl phosphonium chloride[10,11] did not react with the benzophenone under a variety of Wittig procedures. It is known[12] that the Wittig reaction with hindered ketones proceeds with difficulty and the methoxyl groups in the two *ortho* positions of the ketone may be responsible for this hindrance. Using phenyl lithium as the base and refluxing for longer periods yielded a colourless crystalline compound in poor yield but this did not analyse correctly and was not studied further.

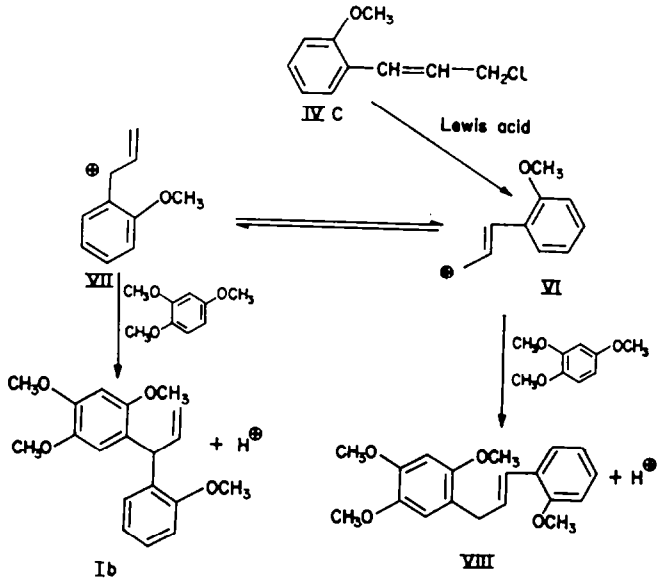
The co-occurrence[13] of dalbergin, latifolin and the quinone 3-methoxy-dalbergenone suggests that biosynthetically they may have a common origin and a proposal[14] was made by Seshadri that C_6 and C_9 units are involved; the coupling here takes place with the α-carbon atom of the C_9 unit whereas in the normal flavonoids the linking is with γ-carbon atom. The nature of the C_9 unit undergoing coupling may however vary, thus a cinnamoyl unit forming 4-phenylcoumarin and cinnamyl unit giving rise to latifolin and thence to the dalbergenones. Both types of coupling probably involve carbonium ions or radicals produced by oxidation mechanism.

After our preliminary communication regarding this synthesis had been sent for publication[15] and completion of the work, Eyton *et al.*[16] proposed a similar biosynthetic origin of the dalbergenones. As possible source of the C_9 unit they mentioned a cinnamyl pyrophosphate, the pyrophosphate group being displaced by a suitable phenol by S_N2 process. No experimental support was, however, provided. Subsequently, they considered[5] Claisen migration as a laboratory analogy for this coupling process. As mentioned earlier we found that with *o*-methoxy (and possibly other) substituent on the "B" ring, Claisen migration did not proceed and hence it may not be a suitable analogy of the coupling process.

Considering the use of the cinnamyl cation mechanism for the biogenesis of latifolin, a combination of *o*-methoxycinnamyl chloride (IVc) (free alcohol was too sensitive) and a Lewis acid was used. As the acceptor of the cinnamyl cation a methoxybenzene rather than a free phenol was selected. Thus when the chloride

[10] G. Wittig and E. Knauss, *Angew Chem.* **71**, 127 (1959).
[11] S. G. Levine, *J. Amer. Chem. Soc.* **80**, 6150 (1958).
[12] S. Trippett and D. M. Walker, *Chem. & Ind.* 990 (1961).
[13] M. M. Rao and T. R. Seshadri, *Tetrahedron Letters* No. 4, 211 (1963).
[14] T. R. Seshadri, *Curr. Sci.* **26**, 239 (1957).
[15] Darshan Kumari, S. K. Mukerjee and T. R. Seshadri, *Curr. Sci.* **34**, 690 (1965).
[16] W. B. Eyton, W. D. Ollis, M. Fineberg, O. R. Gottlieb, I. Salignac De Souza Guimaraes and M. T. Magalhaes, *Tetrahedron* **21**, 2697 (1965).

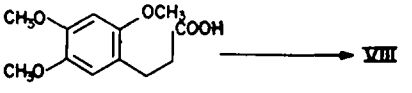
(IVc) in tetrahydrofuran was added slowly to a refluxing solution of 1,2,4-trimethoxybenzene and fused zinc chloride in dry tetrahydrofuran or stirred for a longer time (4 hr) in dry ether at room temperature, a complex mixture, containing about 20% latifolin dimethyl ether (Ib) and about 70% of the benzylstyrene (VIII) along with a large number of minor unidentified compounds, was obtained. The closely related mixture of latifolin dimethyl ether and the benzyl styrene could be separated from other reaction products but separation of these two proved extremely difficult. Eventually pure racemic latifolin dimethyl ether (Ib) was isolated by chromatography and it agreed with the dimethyl ether of the natural sample in UV and IR (CCl_4) spectra and had the same R_f in TLC. The benzyl styrene (VIII) however, could only be obtained pure by using a modified reaction mixture (see later).



A number of other Lewis acids, e.g. aluminium chloride, BF_3-etherate and different reaction conditions were studied in an attempt to improve the yield of the required product but the best so far obtained is only 20–25%. During these studies a number of interesting observations were made. Clearly the reaction proceeds by production of the cinnamyl cation (VI) which undergoes partial isomerization to VII. Electrophilic attack by this mixture on the methoxybenzene then gives latifolin dimethyl ether (Ib) along with the benzylstyrene (VIII). That the composition of this mixture is not controlled thermodynamically is shown by carrying out the reaction in refluxing tetrahydrofuran, dioxan and at ice temperature with zinc chloride, when the composition of the product remained practically unaltered. In one experiment the chloride was added to zinc chloride and the mixture allowed to stand for some time before adding trimethoxybenzene in order to find out whether the composition of the cationic mixture changes with time, but the only observed difference was that more polymeric side products were formed. Hence the rate of equilibration is very rapid.

The cinnamyl cation (VI) is formed by S_N1 process as shown by solvolytic experiments in ether and in dimethylsulphoxide when only the benzylstyrene (VIII) was produced, albeit slowly (max. after 3 days) but no trace of latifolin dimethyl ether could be found; the observation indicates that a Lewis acid is essential for the isomerization of the cation (VI) to VII. Probably traces of free acid are also essential as was found in one experiment in which aluminium chloride was used with dry calcium carbonate to maintain acid free conditions. This combination gave a very good yield of the benzylstyrene (VIII) alone, with some easily separable minor products but no latifolin dimethyl ether. In fact it was from this reaction that we are able to isolate the pure benzylstyrene (VIII), However, it is possible that calcium carbonate prevents the formation of the isomeric cation (VII) by some other mechanism not yet understood since it was found that a combination of zinc chloride with zinc carbonate failed to act in the same way and produced again a mixture of VIII and Ib. Since the above combination is a very good reagent for the synthesis of benzylstyrenes and their biogenetic importance has been emphasized by Gregson *et al.*[17] we are currently investigating the full scope of this reaction.

2-Methoxy-(2′,4′,5′-trimethoxybenzyl)styrene (VIII) isolated from the above reaction had the expected properties and its identity was further confirmed by comparison with a sample prepared in a more unambiguous way using Perkin reaction with 2,4,5-trimethoxydihydrocinnamic acid[18] (IX) and *o*-methoxybenzaldehyde.



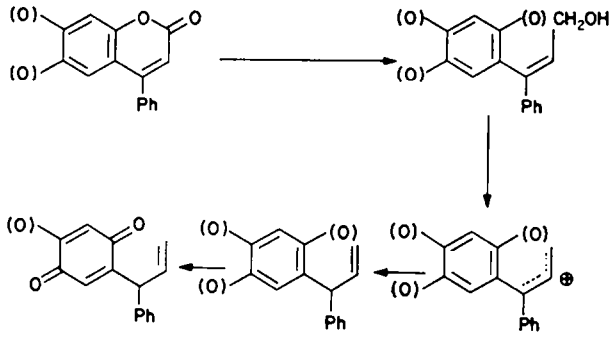
IX

Although the above coupling reaction is successful through ionic intermediates the possibility of radicals being involved in the actual biosynthetic process cannot be overlooked, especially since it is very well known that radicals from cinnamyl alcohols are involved in a large number of biosynthetic processes, e.g. formation of lignin and lignans. However, an attempted coupling reaction between monomethyl resorcinol and *o*-allylanisole in the presence of alkaline ferricyanide was not successful.

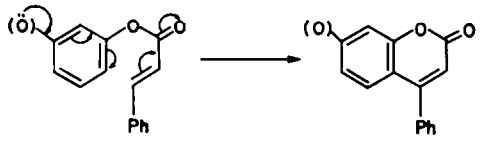
Eyton *et al.*[16] have expressed the view that a γ,γ-diphenylallyl skeleton arising from a cinnamyl pyrophosphate (C_9) and phenol (C_6) undergoes oxidation to quinones (dalbergenones) on the one hand or oxidative ring closure on the other involving the allyl group to 4-phenylcoumarins and thence to benzophenones. While the suggestion is acceptable, there is no known method of ring closure to a coumarin involving an allyl side chain. In fact such a ring closure would favour the β-carbon (to a furanoid) rather than γ-carbon.

It is equally plausible to suggest a reduction and then an oxidation sequence of steps for the origin of dalbergenones from 4-phenylcoumarins through γ,γ-diphenylallyl (latifolin) skeleton as follows:

[17] M. Gregson, W. D. Ollis and O. R. Gottlieb, in press.
[18] C. W. Moore, *J. Chem. Soc.* 1048 (1911).



This reductive origin of latifolin type from 4-phenyl-coumarins is equally well supported by the idea of Birch[19] that natural allylphenols arise from cinnamyl alcohols and the process is aided by the oxygen substituents at *ortho* and *para* positions (both substituents are present in dalbergin). The 4-phenylcoumarins themselves might arise from oxidative coupling of cinnamic esters as shown below. Further oxidation of 4-phenylcoumarins to benzophenones is a natural sequence. Thus we consider that



the same cinnamoyl coenzyme A[20] which gives rise to the large and important branch of flavonoids by a C-acylation sequence also gives rise, by an O-acylation sequence to the 4-phenylcoumarins, γ,γ-diphenylallyl compounds (latifolin type) and dalbergenones. There is support for this idea from the recent observation[21] that a flavanone. liquiritigenin, occurs with dalbergin, latifolin and dalbergenone in *D. latifolia*. Here both the processes must be taking place simultaneously. The formation of benzyl styrenes require a deviation from the sequence; the concerned steps will be a prior reduction of cinnamoyl to cinnamyl unit and C-alkylation by it of a reactive phenol.

EXPERIMENTAL

TLC was done on silica gel G with acetone–pet. ether (10:90) as developing solvent R_L indicates R_f with respect to latifolin dimethyl ether as standard.

cis-o-*Hydroxycinnamyl alcohol* (IVa)

Karrer and Banerjea's[7] method of adding coumarin to LAH did not give the alcohol but instead a colourless compound m.p. 240°. Hence the following procedure of reverse addition was employed

A well stirred solution of coumarin (8 g) in dry ether (200 ml) was treated dropwise with a suspension of LAH (4 g) in the same solvent (100 ml) at 10–15° during the course of 45 min. After stirring for a further 3 hr, the excess LAH was decomposed (sat. NH_4Claq) and the ether layer separated. Extraction with dil. NaOH, acidification and re-extraction with ether furnished an oil

[19] A. J. Birch, *Biosynthetic Pathways in Chemical Plant Taxonomy* (Edited by T. Swain) p. 141. Academic Press (1963).

[20] H. Grisebach and W. D. Ollis, *Experientia* **17**, 4 (1960); A. C. Neish, *Cinnamic Acid Derivatives as Intermediates in the Biosynthesis of lignin and Related Compounds in formation of Wood in Forest Trees* p. 219. Academic Press (1964).

[21] G. D. Bhatia, S. K. Mukerjee and T. R. Seshadri, *Ind. J. Chem.* **3**, 422 (1965).

(2·6 g) which crystallized from AcOEt–benzene as colourless long rectangular prisms, m.p. 110–111°, λ_{max}^{EtOH} 242 mμ (4·04) and 292 mμ (3·63) in agreement with the data reported by earlier workers.

cis-o-*Methoxycinnamyl alcohol*

Compound IVa (200 mg) in dry acetone (20 ml) containing MeI (1·5 ml) was refluxed for 4 hr with anhydrous K_2CO_3 (2 g). The product, a brownish viscous liquid (200 mg), was purified to a colourless viscous liquid by percolation through a short column of alumina. It failed to crystallize but TLC showed it to be a single substance λ_{max}^{EtOH} 242 mμ (3·80), 292 mμ (3·43); ν_{max} film 3550 cm^{-1} (OH); 1610 cm^{-1} (double bond). Its 3,5-dinitrobenzoate crystallized from benzene as pale yellow stout needles m.p. 165–66°. (Found: C, 57·2; H, 4·1. Calc. for $C_{17}H_{14}O_7N_2$: C, 57·0; H, 3·9%.)

γ-(o-*Methoxyphenyl*) *propanol*

Catalytic hydrogenation of *o*-methoxycinnamyl alcohol (100 mg) yielded the propyl alcohol (80 mg) as a colourless viscous liquid, λ_{max}^{EtOH} 275 mμ. Its 3,5-dinitrobenzoate crystallized from benzene as pale yellow tiny prisms, m.p. 115–116°. (Found: C, 56·3; H, 4·6. $C_{17}H_{16}O_7N_2$ requires: C, 56·6; H, 4·4%.)

cis-o-*Methoxycinnamyl chloride*

An ice cold, stirred solution of the *o*-methoxy alcohol (0·5 g) in dry ether (25 ml) containing dry pyridine (0·5 ml) was treated dropwise with an ethereal solution (5 ml) containing freshly distilled $SOCl_2$ (1 ml, excess) during the course of 30 min. The mixture was stirred and occasionally shaken for a further 1 hr and then poured into ice cold dil. HCl. The ether layer was separated and the acid layer extracted twice with more ether and the extracts combined. After washing with cold $NaHCO_3$aq the ether solution was dried and evaporated yielding the chloride as a straw coloured liquid. Attempted distillation led to resinification. It gave a precipitate with alcoholic $AgNO_3$; $\lambda_{max}^{cyclohexane}$ 247·5 and 291 mμ. In IR (liquid film) it showed absence of OH peak and a strong band at 750 cm^{-1} indicative of C—Cl group.

Attempted condensation of monomethyl resorcinol with o-*methoxycinnamyl chloride*

(a) Monomethyl resorcinol (250 mg) and the cinnamyl chloride (350 mg) in dry acetone (40 ml) was refluxed with anhydrous K_2CO_3 (3 g) for 20 hr. The mixture on working up gave the following: (i) NaOH-soluble fraction (110 mg) shown by TLC to be unchanged phenol, (ii) NaOH-insoluble fraction (160 mg) showing hydroxyl absorption in the IR spectrum and from TLC found to be a mixture which resisted all attempts to yield any crystalline product.

(b) A suspension of the dry Na salt of monomethyl resorcinol (from 1·5 g resorcinol) in 1,2-dimethoxyethane (30 ml) containing the chloride (500 mg) was heated under reflux for 24 hr. The cooled solution was diluted with water (200 ml) and extracted with ether. The ether extract contained only 300 mg of alkali-insoluble matter which was also a mixture and did not yield any crystalline product.

3-*Methoxyphenyl*-2-*tosyloxycinnamyl ether* (Vb)

A mixture of 2-tosyloxycinnamyl bromide (3·5 g) and resorcinol monomethyl ether (2 g) in acetone (50 ml) was refluxed with anhydrous K_2CO_3 (10 g) for 10 hr. After distilling off acetone the cinnamyl ether (1·7 g) was extracted with ether; it crystallized from AcOEt–light pet. as colourless rhombs, m.p. 70–71°, λ_{max}^{EtOH} 252 mμ (3·22); ν_{max}^{KBr} 1600 cm^{-1} (double bond), 1375 cm^{-1} (tosyloxy). (Found: C, 67·5; H, 5·6. $C_{23}H_{22}O_5S$ requires: C, 67·3; H, 5·3%.)

Hydrolysis and methylation of (Vb) *to* 3-*methoxyphenyl* 2-*methoxycinnamyl ether* (Va)

The tosyl compound (1·7 g) in pyridine (5 ml) and NaOHaq (10%; 10 ml) was stirred at 50° for 4 hr, then diluted with water (100 ml) and acidified. The precipitated substance was taken up in ether, ether solution washed with dil. HCl and the product extracted with NaOH. On precipitation with acid a gum (0·9 g) was obtained; it failed to crystallize and was therefore directly methylated by refluxing for 5 hr with Me_2SO_4 (1 ml) and K_2CO_3 (3 g) in anhydrous acetone (25 ml). The alkali-insoluble brownish gummy methylation product (0·8 g) showed one major spot (R_f = 0·7) and a number of other minor spots on TLC. Chromatography, on alumina (15 g) impregnated with

$AgNO_3$ (6·7 g) and elution with pet. ether, gave in the first 60 ml only a gummy substance. The next 140 ml of eluate contained only the methyl ether (0·6 g; TLC R_f 0·7) and it crystallized from MeOH as colourless clusters of long needles m.p. 59–60°, λ_{max}^{EtOH} 255 mμ (4·23), 285 mμ (3·90) and 300 mμ (3·82); ν_{max}^{nujol} 1640 cm^{-1} (double bond). (Found: C, 75·5; H, 6·8. $C_{17}H_{18}O_3$ requires: C, 75·5; H, 6·6%.)

Ozonolysis of this methyl ether in AcOEt gave *o*-methoxybenzaldehyde (m.p. and mixed m.p. of 2,4-dinitrophenyl hydrazone 252–253°) as the only identifiable fragment..

Attempted Claisen migration of the cinnamyl ether (Va)

(a) The ether (50 mg) was heated under red. press. at 225° in a metal bath for 4 hr. The resulting brown gum did not yield any alkali-soluble product. TLC showed it to be essentially the starting compound.

(b) Dimethyl aniline (5 ml) containing the ether (100 mg) was refluxed for 12 hr. On working up, no alkali-soluble substance could be isolated.

(c) The above experiment was repeated using diethyl aniline as the medium. After 48 hr of reflux, no alkali-soluble product could be isolated and polymerization took place. In another run the use of small amounts of NH_4Cl did not produce any improvement.

(d) The tosyl ether (200 mg) was heated under red. press. at 190° for 1 hr. No tangible product could be isolated from the resulting dark polymeric mass.

Wittig reaction of 2,2',4,5-*tetramethoxybenzophenone*

A suspension of triphenyl methoxymethyl phosphonium chloride (0·6 g) in dry ether (10 ml) was treated in an atmosphere of N_2 with PhLi in dry ether (3·5 ml, 2·1 mmoles) and the mixture shaken at room temp when an orange red colour developed. After 5 min a solution of 2,2',4,5-tetramethoxybenzophenone (500 mg, 1·6 mmoles) in ether (10 ml) was added and the mixture stirred for 2 hr and then filtered from the sludge. The ether solution was washed with water, dried and the ether evaporated giving a viscous liquid (550 mg). It was chromatographed over basic alumina (activity I, 30 gm). Elution first with benzene–light petrol [(10:90); 100 ml] gave triphenyl phosphine oxide (400 mg) m.p. 152–154°. Further elution with benzene–light petrol (50:50; 100 ml) gave a crystalline compound (45 mg) which came out from the same mixture as colourless rectangular plates m.p. 174–175°, λ_{max}^{EtOH} 297 mμ; ν_{max}^{nujol} 1610 cm^{-1} (double bond), 1270 cm^{-1} (enol ether). (Found: C, 64·2; H, 7·4; $C_{19}H_{22}O_5$ requires: C, 69·1; H, 4·7%.) Since the results did not agree with the requirement of the enol ether, the product was not investigated further.

Condensation of o-*methoxycinnamyl chloride and* 1,2,4-*trimethoxy benzene*

A number of catalysts and reaction conditions were examined (Table I). A typical run is described here.

The chloride (500 mg) in dry ether (50 ml) was added slowly to a stirred solution of the trimethoxybenzene (500 mg) and fused $ZnCl_2$ (1 g) in the same solvent (50 ml) at 0°. After 2 hr the blue coloured mixture was poured into a mixture of ice and HCl, shaken thoroughly and the ether layer separated, washed with dil. HCl, then with dil. $NaHCO_3$aq and with water and finally dried. Evaporation of the ether gave a colourless viscous liquid (820 mg). TLC showed it to be a complex mixture of 13 substances of which two were very prominent $R_L = 1$, (20%) and $R_L = 0{\cdot}88$, (70%); the rest about (10%). Co-chromatography established that the faster moving one ($R_L = 1$) was latifolin dimethyl ether. Separation of these two major components of this mixture is described later.

Separation of latifolin dimethyl ether from zinc chloride catalysed reaction mixture

The mixture (820 mg) was first chromatographed on basic alumina (activity I; 80 g). After a preliminary wash with benzene–light petroleum (30:70; 150 ml) to remove most of the unreacted trimethoxybenzene, the column was eluted with benzene–light petroleum (50:50; 100 ml) when a mixture (350 mg) of latifolin dimethyl ether and the benzyl styrene along with a small amount of trimethoxybenzene and traces of other compounds were obtained. No attempt was made to elute all the latifolin dimethyl ether and the benzyl styrene present in the original mixture as this inevitably resulted in desorption of all other undesired substances from the column and made subsequent separations impossible.

TABLE I

Sl. No.	Catalyst	Temp	Time (hr)	Medium	Yield %[a] L.D.M.E. $R_L = 1$	Yield %[a] Benzyl[b] styrene $R_L = 0{\cdot}88$	Yield %[a] Others
1.	Anh. $AlCl_3$	0°	2	Ether	15	70	15
2.	Anh. $ZnCl_2$	0°	2	Ether	25	65	10
3.	BF_3-ethereate	0°	4	Ether	20	70	10
4.	Anh. $ZnCl_2$	65°	3	THF	25	65	10
5.	Anh. $ZnCl_2$	80°	3	Dioxan	20	70	10
6.	$AlCl_3 + CaCO_3$	0°	24	Ether	—	80	20
7.	$ZnCl_2 + ZnCO_3$	0°	24	Ether	10	80	10
8.	—	25°	72	dimethyl sulphoxide	—	20	80
9.	—	25°	72	Ether	—	10	90

[a] Estimations are visual and approximate based on the intensity and area of spots on TLC plates.
[b] 2′,4′,5′-trimethoxybenzyl-2-methoxystyrene (VIII).

The above mixture (350 mg) was next chromatographed on a column of silica gel (40 g) impregnated with $AgNO_3$ (6 gm). Elution first with ether–light petroleum (10:90; 75 ml) removed trimethoxybenzene along with small amounts of benzyl styrene. On increasing the concentration of ether in the eluant to 20% the benzyl styrene was eluted together with small amounts of latifolin dimethyl ether. After elution with 120 ml of this mixture, the concentration of ether was raised to 50% and this (70 ml) eluted a gum (60 mg) which was rich in latifolin dimethyl ether but still contained small amounts of benzyl styrene.

This mixture (60 mg) was rechromatographed on a similar column (10 g) and two fractions were collected using ether–light petroleum (15:85). The first fraction (70 ml) gave again a mixture but the second fraction (140 ml) gave a product (30 mg) which contained only traces of benzyl styrene. On keeping this in MeOH in the cold for several days latifolin dimethyl ether crystallized out slowly. Recrystallization from light petroleum gave the racemic methyl ether as colourless stout prisms m.p. 64–65°. Its UV and IR (CCl_4) spectra were superimposable with those of the dimethyl ether of natural latifolin and on TLC the two compounds were indistinguishable.

2-Methoxy-(2′,4′,5′-trimethoxybenzyl) styrene (VIII)

(a) Separation of the benzyl styrene (VIII) from the "aluminium chloride calcium carbonate" reaction product was carried out as follows.

The mixture (200 mg) was first chromatographed on basic alumina (20 g). The eluate (140 mg) with benzene–light petroleum (50:50; 100 ml) contained impurities which could only be removed by rechromatography on silica gel impregnated with $AgNO_3$ (20 g). Rapid elution with pet. ether (100 ml) then gave the benzyl styrene (45 mg) which crystallized from dil MeOH as colourless aggregates of plates m.p. 56–57°; λ_{max}^{EtOH} 250 mμ (4·23), 260 mμ (4·15) and 295 mμ (4·03); ν_{max}^{nujol} 1640 cm^{-1} (double bond). (Found: C, 73·1; H, 7·3. $C_{19}H_{22}O_4$ requires: C, 72·6; H, 7·0%.)

(b) 2,4,5-Trimethoxydihydrocinnamic acid (100 mg) and *o*-methoxybenzaldehyde (100 mg) in Ac_2O (1·5 ml), containing fused AcONa (1 g), was heated at 180–190° for 12 hr. The product, gave the benzyl styrene (8 mg) in poor yield, m.p. 56–57° alone or when mixed with the sample described above. The UV spectra of both were also identical.