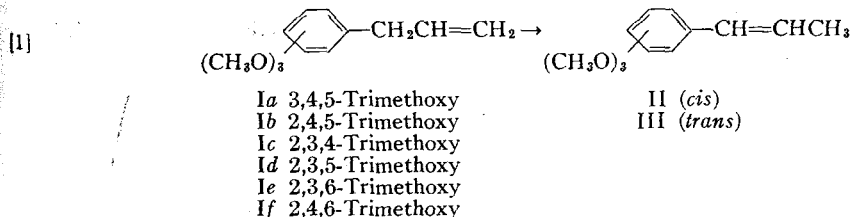5. V. Evdokimoff and A. Calo. Ann. Chim. Rome, **49**, 1321 (1959).
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SYNTHESIS OF THE TRIMETHOXYPHENYLPROPENES

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In the reaction shown in eq. [1] eighteen compounds are represented, of which four (elemicin (1), I*a*; isoelemicin (2), III*a*; asarone (3), III*b*; and β-asarone (4), II*b*), as well as an undesignated "calamol" (5), have been observed as constituents of essential oils, and another four have, in addition, been encountered synthetically as chemical intermediates (6). The syntheses and physical properties of these and of the ten remaining

[1]

I*a* 3,4,5-Trimethoxy
I*b* 2,4,5-Trimethoxy
I*c* 2,3,4-Trimethoxy
I*d* 2,3,5-Trimethoxy
I*e* 2,3,6-Trimethoxy
I*f* 2,4,6-Trimethoxy

II (*cis*)
III (*trans*)

isomers are described in this note. The methylation of the Claisen rearrangement product of allyl 2,6-dimethoxyphenyl ether yielded elemicin (I*a*) which was identical with that isolated from nutmeg oil (7), and the 2,4,6 counterpart (I*f*) has been synthesized (6*a*) by methylation of the rearrangement product of allyl 3,5-dimethoxyphenyl ether. The synthesis of 2,3,4-trimethoxyallylbenzene (I*c*) was achieved through the corresponding rearrangement of allyl 2,3-dimethoxyphenyl ether (6*b*), but it has been neither isolated nor characterized.

The three remaining isomers, I*b*, I*d*, and I*e*, were obtained by the thermal rearrangement of the appropriate allyl dimethoxyphenyl ethers, followed by methylation of the potassium salts of the resulting phenols with methyl iodide. In the first of these, the rearrangement of allyl 3,4-dimethoxyphenyl ether to the phenolic precursor of I*b*, there are two ortho positions available. Rearrangement occurred preferentially (7:1) to the side nonadjacent to the methoxyl group, as shown by eventual conversion into asarone (III*b*) which was identical with that obtained from parsley oil. In the latter two required rearrangements (those of allyl 2,4-dimethoxyphenyl ether and allyl 2,5-dimethoxyphenyl ether to yield the phenolic precursors to I*d* and I*e* respectively), only a single ortho position is available for the migrating allyl group. The first of these ethers, indeed, rearranged exclusively (>95%) to the available ortho position, but the second underwent appreciable para rearrangement (57% ortho, 43% para) as well as diallylation through some intermolecular phenomenon (see Experimental).

Twelve isomers (II*a*–II*f*; III*a*–III*f*) can result from the base-catalyzed isomerization of the six trimethoxyallylbenzenes, I*a*–I*f*. II*b*, III*a*, and III*b* have been mentioned above as natural products, and both III*c* and III*f* have been prepared synthetically (6). The six allyl isomers described above have each been isomerized in ethanolic potassium hydroxide to mixtures of their *cis*- and *trans*-propenyl counterparts. The ratio of isomers that are formed invariably favored the *trans* form, which further was found to be the slower moving component in gas–liquid chromatography (g.l.c.) separations (8) and to be, in all cases except one, a crystalline solid at or near room temperature. The isomers were purified by preparative g.l.c., and only materials so obtained were utilized for the physical data recorded in Table I.

TABLE I

Physical characteristics of the eighteen trimethoxyphenylpropenes

Methoxy position	Alkyl group	Refractive index*	Melting point (°C)†	Retention time (min)‡	Isomer ratio, *trans/cis*§
3,4,5	Allyl	1.5308		2.38	11.4
	cis-Propenyl	1.5487		2.78	
	trans-Propenyl	1.5572	17–18	3.94	
2,4,5	Allyl	1.5317		2.59	11.5
	cis-Propenyl	1.5559		3.27	
	trans-Propenyl	1.5652	57–58	4.70	
2,3,4	Allyl	1.5174		1.37	5.4
	cis-Propenyl	1.5345		1.69	
	trans-Propenyl	1.5460	25–26	2.28	
2,3,5	Allyl	1.5240		2.24	13.4
	cis-Propenyl	1.5394		2.53	
	trans-Propenyl	1.5495	44–45	3.68	
2,3,6	Allyl	1.5238		1.73‖	12.2
	cis-Propenyl	1.5340		1.78‖	
	trans-Propenyl	1.5529		2.81	
2,4,6	Allyl	1.5306		2.62	5.8
	cis-Propenyl	1.5342		3.86	
	trans-Propenyl	1.5638	72–73	5.32	

*All values measured with the sodium D line at 24.5 °C. Solids were supercooled.
†Uncorrected.
‡Determined on a 20M polyethylene glycol column, described in the Experimental. 1,2,3-Trimethoxybenzene was added to the test mixtures, and its retention time taken as 1.00.
§Determined from the areas of the appropriate peaks, as measured by a rolling-disk planimeter.
‖Complete separation is obtained when a SE-30 silicone substrate is employed.

EXPERIMENTAL

The g.l.c. separations were achieved on a Wilkens Instrument Company Autoprep A-700. The principal column employed was an aluminium column, 5 ft by $\frac{3}{8}$ inch diameter, loaded to 10% with 20M polyethylene glycol on 60/80 mesh Chromosorb W. At an air bath temperature of about 180 °C and with a helium flow of about 500 ml/min, the standard internal reference chemical, 1,2,3-trimethoxybenzene, required about 4 min to emerge. The retention times of materials summarized in this report may thus be estimated from the values in Table I. Other substrates employed in the work will be described as they are mentioned. Samples for microanalytical evaluation were obtained from the g.l.c. separation directly in sealable capillaries. The members of this series all carry the empirical formula $C_{12}H_{16}O_3$, and all analyses were acceptable.

All infrared spectra were recorded on a Beckman IR-5A spectrophotometer. With the exception of the three higher melting *trans*-propenyl isomers, all samples were recorded as films between salt plates. These eighteen spectra have been placed in The Depository of Unpublished Data.* The physical data are given in Table I.

All materials described in this report were synthesized by the general sequence of reactions: dimethoxyphenol → allyl dimethoxyphenyl ether → allyldimethoxyphenol → trimethoxyallylbenzene (I) → trimethoxypropenylbenzene (II and III). As it would be unnecessarily repetitious to describe all six parallel processes,

*Photocopies may be obtained upon request to: The Depository of Unpublished Data, National Science Library, National Research Council, Ottawa, Canada.

only one will be presented in detail. Any significant deviations required in the other isomeric syntheses will be mentioned briefly.

2,4-Dimethoxyphenol

A solution of 68 g of 2,4-dimethoxybenzaldehyde (K and K Laboratories) in 250 g glacial acetic acid was brought to 25° and treated dropwise, over 1 h, with 86 g of a 40% solution of peracetic acid in acetic acid. The reaction mixture was diluted with three volumes of water, and then neutralized cautiously with 283 g of anhydrous potassium carbonate. Extensive extraction with ether yielded, after removal of the solvent, 66 g of the formate of 2,4-dimethoxyphenol. This was hydrolyzed with 10% base for 1 h at steam bath temperatures. The resulting solution was extracted once with methylene chloride (discarded), acidified with aqueous hydrochloric acid, and re-extracted several times with methylene chloride. These latter extracts were washed once with an aqueous solution of sodium bicarbonate (which removed much of the color), dried, and concentrated by evaporation on the steam bath. The resulting product, which crystallized when the concentrate was cooled below room temperature, weighed 34.4 g (54% yield) and yielded a benzoate (with benzoyl chloride in pyridine, recrystallized from cyclohexane) which melted at 89–90 °C (literature values: phenol, m.p. 28°; benzoate, m.p. 90° (9)). The 2,3-, 3,4-, and 2,5-dimethoxybenzaldehydes were oxidized similarly to the phenols, in similar yields. 3,5-Dimethoxybenzaldehyde gave no phenolic product with peracetic acid, and the corresponding phenol was synthesized from phloroglucinol (10). 2,6-Dimethoxyphenol was obtained commercially from Eastman Kodak Company.

Allyl 2,4-Dimethoxyphenyl Ether

A solution of 31.0 g of the above crude phenol in 60 ml absolute ethanol was combined with another containing 11.25 g potassium hydroxide in 90 ml anhydrous ethanol. Allyl bromide was immediately added (28 g) and the resulting solution refluxed on the steam bath for 2 h. A precipitate of potassium bromide formed within a minute of heating. At the end of the reaction, the mixture was quenched with several volumes of water, made strongly basic with 10% caustic, and extracted with several volumes of ether. Evaporation of the solvent provided 33.2 g of the desired product (85% yield; b.p. 107–110° at 1.0 mm Hg; $n_D^{22.8}$ 1.5322), which was shown to be free of the starting phenol by analysis on an ethylene glycol succinate g.l.c. column (5% substrate, 10 ft length, $\frac{3}{8}$ inch diameter, 165°*).

2-Allyl-4,6-dimethoxyphenol

The ether (31.0 g) was heated to 215 °C, at which temperature an exothermic reaction ensued that raised the temperature to 270°. The temperature was held at about 260° for an additional 10 min. The rearrangement product thus obtained (n_D^{25} 1.5464) was submitted to methylation without further purification.†

2,3,5-Trimethoxyallylbenzene (Id)

The phenol was methylated directly, in anhydrous ethanol, by treatment with, first, 8.7 g potassium hydroxide dissolved in 75 ml boiling ethanol, and then with 22.4 g methyl iodide. Potassium iodide formed immediately. After 3 h at reflux, the reaction mixture was cooled, quenched with several volumes of water, made strongly basic with 10% caustic, and then extracted with four portions of 100 ml ether. These extracts, after drying and removal of the solvent by evaporation, provided 28 g of an oil. Analysis by g.l.c. showed the presence of about 10% 1,2,4-trimethoxybenzene (from the 2,4-dimethoxyphenol known to be present before methylation) and less than 2% of all other volatile contaminants. The yield of Id was thus greater than 80% based on the initial allyl ether. The infrared spectra of the crude reaction product and of the chromatographically isolated specimen were virtually identical; the latter was employed for the refractive index value.

The 2,3,6-trimethoxy isomer obtained similarly from allyl 2,5-dimethoxyphenyl ether was admixed with an almost equal amount of the 2,4,5-isomer. To obtain an adequate amount of the former material both for necessary descriptions and for the subsequent isomerization to the propenyl mixture, it was necessary to repeatedly inject scores of 0.15 ml portions into the Wilkins Autoprep machine, utilizing the existing trapping machinery. Trapping efficiency was less than 50%, because of extensive aerosol formation. In this process, a later peak, constituting 12% of the entire crude reaction mixture, was trapped. This trimethoxy-diallylbenzene showed a $n_D^{24.5}$ of 1.5228.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.11; H, 7.66.

As one might expect the 1,2,4-substitution of the starting ether to be maintained, and as one might assume that the two allyl groups are located either ortho–ortho or ortho–para to the formed hydroxyl group, then these two allyl groups must bear a meta relationship to one another. Thus this material is assigned the structure 1,3-diallyl-2,4,5-trimethoxybenzene.

*It has been found that the thermally unstable allyl ethers can be analyzed if chromatographed on an ethylene glycol succinate column at temperatures below 180°. Under these conditions there is no detectable rearrangement to the allyl phenols. With a silicone column, even at these temperatures, there is extensive continuous rearrangement on the column, providing a complex and misleading picture of the original composition.

†The presence of about 10% of 2,4-dimethoxyphenol in this product (a material specifically shown to be absent in the ether precursor) indicates a side reaction involving deallylation. The phenol is best removed as its methyl ether (1,2,4-trimethoxybenzene) in the next step.

2,3,5-Trimethoxypropenylbenzene (IId and IIId)

A solution of 26 g of the crude trimethoxyallylbenzene in an equal weight of anhydrous ethanol was treated with 52 g finely flaked potassium hydroxide. Heating on the steam bath for 24 h with occasional agitation effected complete isomerization to the propenyl mixture. The reaction mixture was quenched with much water, and extracted with ether. Removal of the solvent provided 24.6 g of the crude mixture, a yield of about 95%. This crude product provided the isomer ratio data incorporated in Table I. Dilution with an equal volume of pentane, intense cooling, and rapid filtration yielded 9.2 g of an amber-colored crystalline solid. This, upon recrystallization from hexane, provided the pure *trans* isomer, m.p. 44–45°. The mother liquors of the original pentane crystallization were stripped of solvent, and then subjected to g.l.c. purification to provide the sample of the *cis* isomer described in this note. The 2,3,4- and 2,4,6-tri-methoxyallylbenzenes required twice the time for isomerization.

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DIRECT DISPLACEMENT OF A PRIMARY TOLYL-*p*-SULFONYLOXY GROUP BY THE METHOXIDE ION: A MORE DIRECT ROUTE TO 5-*O*-METHYL-L-ARABINOSE AND 3,5-DI-*O*-METHYL-L-ARABINOSE

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The direct displacement (S_N2) of a primary tosyloxy group by many other groups has been known for some time. Mitra *et al.* (1) have reported the displacement of a primary mesyloxy (methanesulfonyloxy) group in a hexose derivative by methoxide ion, and we now report the displacement by methoxide of the primary tosyloxy group in a pentose derivative.

Detosylation of 5-*O*-tosyl-L-arabinose derivatives with aqueous methanol and sodium amalgam (2, 3) to give the free hydroxyl on C-5 invariably produced traces of the methylated sugar. It was felt that reaction with sodium methoxide in anhydrous methanol should increase the yield of this methylated sugar by a reaction analogous to that described by Mitra *et al.* (1). Under these conditions 1,2-*O*-isopropylidene-5-*O*-tosyl-L-arabinose (I; R = H, R_1 = tosyl) gave equal amounts of 1,2-*O*-isopropylidene-5-*O*-methyl-L-arabinose (I; R = H, R_1 = CH_3) and 1,2-*O*-isopropylidene-L-arabinose (I; R = R_1 = H), while reaction with 1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-tosyl-L-arabinose (I; R = CH_3, R_1 = tosyl) gave four times as much 3,5-di-*O*-methyl-L-arabinose derivative (I; R = R_1 = CH_3) as 3-*O*-methyl-L-arabinose derivative (I; R = CH_3, R_1 = H).

The reaction of methyl 3,4-di-*O*-methyl-2-*O*-tosyl-β-L-arabinoside (II; R_2 = tosyl, R_3 = R_4 = CH_3) under the same conditions (sodium methoxide in anhydrous methanol) gave mainly methyl 3,4-di-*O*-methyl-β-L-arabinoside (II; R_2 = H, R_3 = R_4 = CH_3)

3