Meta Substitution in Electrophilic Benzylations of 2,6-Dimethylphenol and Alkyl 2,6-Dimethylphenyl Ethers: Product Distributions and Mechanism

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Electrophilic benzylations of 2,6-dimethylphenol and 2,6-dimethylanisole under a variety of conditions yield ca. 40% and 70%, respectively, of the meta substitution products, although other electrophilic substitution reactions appear to proceed exclusively at the para positions. Similar results were obtained with other alkyl 2,6-dimethylphenyl ethers and with 2,6-diallylanisole. A variety of possible mechanisms were investigated and shown to be inadequate, leading to the conclusion that meta substitution proceeds by direct attack at the normally unreactive meta positions.

Hydroxy and alkoxy substituents on aromatic rings are extremely effective in directing attack of electrophilic reagents to positions on the rings ortho or para to the substituents. Indeed, a search of the literature has failed to reveal a single instance of an electrophilic substitution reaction of a simple phenol or aryl ether with unsubstituted positions ortho or para to the oxygen atoms in which significant amounts of meta substitution occurred.

Even in reactions of 2,6-dimethylphenol (2,6-DMP), in which the two meta positions compete only with the single para position, and in which the two methyl groups direct substitution to positions meta to the hydroxy group, electrophilic bromination,[1] chlorination,[2] nitration,[1] sulfonation,[3] disulfuration[4] (with sulfur dichloride and sulfur), and alkylation with several alkylating agents[5] have all been reported to yield products of attack at the para position (C-4), with no reports of detection of any meta substitution products.

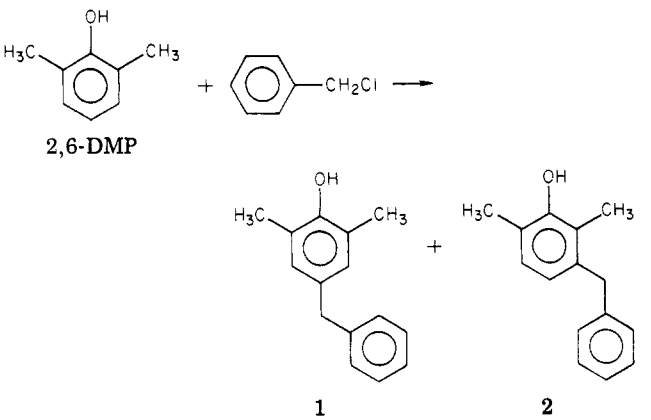
Electrophilic substitution reactions of 2,6-dimethylanisole (2,6-DMA) have been less extensively studied than those of 2,6-DMP. However, both acylation[1] and bromination[6] of 2,6-DM have been reported to yield solely para substitution products.

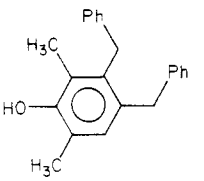
It was therefore with appreciable confidence that, in the course of another study, we attempted to prepare 4-benzyl-2,6-dimethylphenol (1) by the zinc chloride catalyzed Friedel–Crafts reaction of 2,6-DMP with benzyl chloride. Our confidence was misplaced. The *m*-benzyl isomer (2) was found to comprise nearly 40% of the reaction products. Furthermore, benzylation of 2,6-DMA under the same conditions resulted *predominantly* (ca. 70%) in benzylation at the meta positions.

In this paper we report on the products and mechanism of Friedel–Crafts benzylations of 2,6-dialkylphenols and alkyl 2,6-dialkylphenyl ethers.

Products of Friedel–Crafts Benzylations

Reaction of 2,6-DMP with benzyl chloride in refluxing chloroform in the presence of anhydrous zinc chloride gave an initially oily product from which 3,4-dibenzyl-2,6-dimethylphenol (3) crystallized (18% crude yield) when the oil was allowed to stand at room temperature. To avoid problems with polybenzylation, we carried out the reaction as before, employing a 10 M excess of 2,6-DMP. At the end of the reaction, unreacted 2,6-DMP was removed by sublimation or steam distillation to yield a crystalline residue, mp 58.5–65 °C, in 74% yield based on a 1:1 reaction of benzyl chloride and 2,6-DMP. The product could be recrystallized unchanged from benzene or methanol, and gas–liquid chromatography on several columns showed only a single peak. However, gas–liquid chromatography on an Apiezon L column showed two overlapping peaks, with relative retention times of 1.00:1.08.





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The NMR spectrum of the product mixture included two singlets at δ 3.80 and 3.90 in the area ratio 0.63:0.37. These peaks were assigned to the diarylmethylene groups of benzylphenols. The aromatic region of the spectrum showed a doublet of doublets (J = 8 Hz) at δ 6.62 and 6.82 and a singlet at δ 6.75, which were assigned to protons of the phenolic rings of 1 and 2, in addition to phenyl group signals at ca. δ 7.2. The spectrum therefore corresponded to that expected of a mixture of phenols 1 and 2.

Attempts to separate the mixture by crystallization or by column or thin-layer chromatography were unsuccessful. The mixture was therefore reacted with sufficient bromine to brominate the amount of 2 estimated to be present by comparison of the area of the NMR singlet at δ 3.90 with the total area for the δ 3.80 and 3.90 singlets. When this was done, the spectrum of the reaction product

(1) V. Auwers, K.; Markovits, T. *Chem. Ber.* **1908**, *41*, 2332.
(2) Heicken, K. *Angew. Chem.* **1939**, *52*, 263.
(3) Karrer, P.; Leiser, P. *Helv. Chim. Acta.* **1944**, *27*, 678.
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(5) Niederl, J. B.; McCoy, J. S. *J. Am. Chem. Soc.* **1941**, *63*, 1731. van Helden, R.; ter Borg, A. P.; Bickel, A. F. *Recl. Trav. Chim. Pays-Bas* **1962**, *81*, 599. Grant, M. S.; Hickenbottom, W. J. *J. Chem. Soc.* **1959**, 2513.
(6) (a) E.g., Stock, L. M.; Brown, H. C. *Adv. Phys. Org. Chem.* **1962**, *1*, 35. (b) Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc.* **1966**, *84*, 1688, 1695. (c) Olah, G. A. *Acc. Chem. Res.* **1971**, *4*, 240. Tsuge, O.; Tashiro, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 125. (e) Shimao, I. *Nippon Kagaku Zasshi* **1968**, *89*, 895. (f) Olah, G. A.; Kobayashi, S.; Tshiro, M. *J. Am. Chem. Soc.* **1972**, *94*, 7448. (g) DeHaan, F. P.; et al. *J. Am. Chem. Soc.* **1978**, *100*, 5944.

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Table I. Benzylation of 2,6-Dimethylphenol

alkylating agent	catalyst (concn, M)	solvent	temp, °C	rctn time, h	no. of runs	% conversion	% meta benzylation
$C_6H_5CH_2Cl$	$ZnCl_2$[a]	$CHCl_3$	68	16	4	76 ± 4	37.5 ± 1.9
$C_6H_5CH_2Cl$	$CaCl_2$[a]	$CHCl_3$	68	16	1	4	33 ± 2
$C_6H_5CH_2Cl$	$TiCl_4$ (0.1)	CH_3NO_2	26	2	1	64	39.1 ± 0.1
	$TiCl_4$ (0.1)	CH_3NO_2	26	16	1	74	39.4 ± 0.2
$C_6H_5CH_2Cl$	$AlCl_3$ (0.1)	CH_3NO_2	26	0.25	2	81 ± 5	38.4 ± 1.5
$C_6H_5CH_2OH$	H_2SO_4 (ca. 3)	$(C_2H_5)_2O$	~30	2	2	30 ± 4	39.4 ± 2.9
	H_2SO_4 (ca. 3)	$(C_2H_5)_2O$	~30	18	2	71 ± 4	40.6 ± 1.8

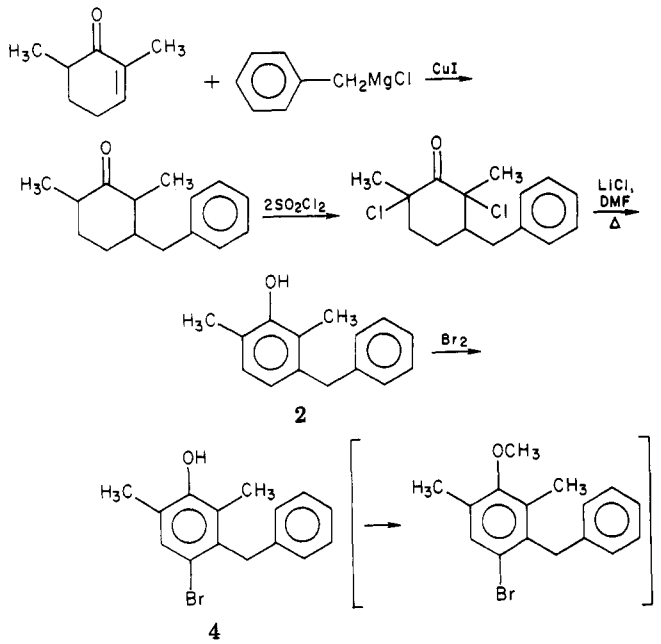
[a] Insoluble solid catalyst.

Table II. Benzylation of 2,6-Dimethylanisole

alkylating agent	catalyst (concn, M)	solvent	temp, °C	rctn time, h	no. of runs	% conversion	% meta benzylation
$PhCH_2Cl$	$ZnCl_2$[a]	$CHCl_3$	68	16	3	84 ± 3	69.7 ± 1.9
$PhCH_2Cl$	$TiCl_4$ (0.1)	CH_3NO_2	26	2	2	59 ± 5	71.6 ± 1.0
$PhCH_2Cl$	$AlCl_3$ (0.1)	CH_3NO_2	26	0.25	1	64	72.3 ± 0.4
$PhCH_2OH$	H_2SO_4 (ca. 3)	$(C_2H_5)_2O$	~30	2	2	14 ± 1	74.2 ± 2.0

[a] Insoluble solid catalyst.

Scheme I. Independent Syntheses of Phenols 2 and 4



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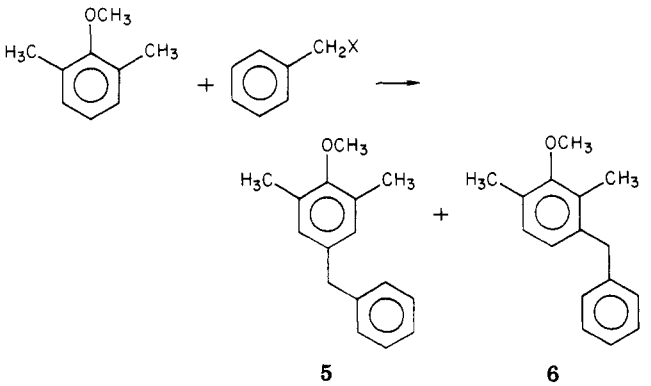
showed the singlets at δ 3.80 and 6.75 assigned to the 4-benzyl isomer 1 to be unchanged, but the singlet at δ 3.90 assigned to 2 was replaced by a singlet of equal area at δ 4.20. The doublet of doublets assigned to the protons of the phenol ring of 2 had disappeared, having been shifted to a position similar to those of the phenyl group protons. The components of the mixture after bromination were readily isolated by gas–liquid chromatography. They were identified by their spectra and by comparison with independently synthesized samples as 1 and 3-benzyl-4-bromo-2,6-dimethylphenol (4). (The procedures for the syntheses of 2 and 4 are outlined in Scheme I). A mixture of 1 and 2 in a 1.5:1 ratio had NMR and IR spectra and VPC behavior identical with those of the mixture obtained from the benzylation of 2,6-DMP.

The evidence described above demonstrates that 4 is obtained by bromination of 2 present in the original Friedel–Crafts benzylation product, and does not arise, for instance, by rearrangement of 1 during the bromination process. Thus, benzylation of 2,6-DMP under the mild conditions employed resulted in formation of ca. 37% of the unexpected meta-benzylation product.

To determine whether the unexpectedly high percentage of meta benzylation was due to the use of the solid, insoluble (in $CHCl_3$) zinc chloride catalyst, we carried out the benzylation of 2,6-DMP employing several different solvents and catalysts. As can be seen in Table I, most of these conditions gave at least as high percentages of the meta benzylation product as did the use of zinc chloride in chloroform.

Benzylation of excess 2,6-DMA under a variety of conditions gave mixtures of the para- and meta-benzyl isomers 5 and 6. In each case the meta-benzyl isomer 6 comprised ca. 70% of the mixture, as determined by the area ratios of the diarylmethylene peaks of 5 and 6. These results are summarized in Table II. It is of interest that in the reaction with benzyl alcohol as the alkylating agent, at least, each individual meta position of 2,6-DMA is more reactive toward benzylation than is the para position, despite the fact that most electrophilic reactions of 2,6-DMA occur exclusively at the para position.



5 6

The products from benzylation of 2,6-DMA, like those from 2,6-DMP, could not easily be separated by physical means. However, when sufficient bromine to react with 6 was added to the product mixture, the diarylmethylene singlet and the peaks assigned to the protons on the anisole ring of 6 were shifted downfield, while no changes occurred in the positions or sizes of peaks assigned to 5. Ether 5 and the 4-bromo derivative of 6 could then easily be isolated by gas–liquid chromatography. There structures were established from their spectra, elemental analyses, and independent syntheses by methylation of 1 and 4.

The reactions of excess *n*-propyl 2,6-dimethylphenyl ether and *n*-hexyl 2,6-dimethylphenyl ether with benzyl

chloride in chloroform catalyzed by zinc chloride were also studied. The NMR spectra of the products again showed that the meta-benzyl isomers were the predominant components of the mixtures obtained. The product ratios seemed similar to those obtained by benzylation of 2,6-DMA, but precise analyses could not be obtained from the spectra, since signals for the methylene groups on oxygen overlapped those for the diarylmethylene protons.

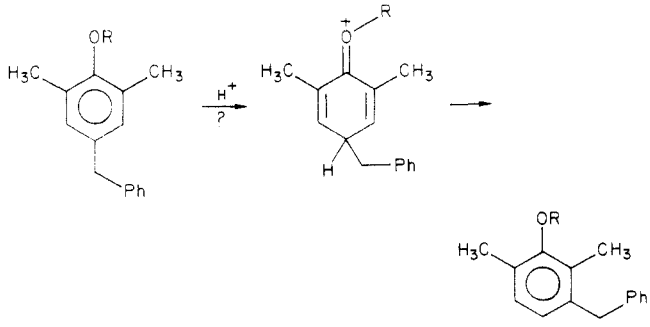
Friedel–Crafts benzylations of 2,6-DMP and 2,6-DMA thus result in much higher percentages of substitution at meta positions than are observed in other electrophilic substitution reactions.[1-5] Benzylations of aromatic molecules are normally less selective than are most other types of electrophilic substitutions,[6] so that a relatively high meta/para ratio is not unexpected. However, the yields of meta substitution products seem far too high to be explained solely on the basis of lack of selectivity of benzylation reagents. Olash's group[5b] has studied benzylations of substituted benzenes in nitromethane, catalyzed by aluminum chloride, while Shimao and his group[5e] have studied similar reactions in excess benzyl alcohol, catalyzed by *p*-toluenesulfonic acid. Hammett calculations based on their data (and the assumption that the σ^+ value for an ortho-methyl substituent is similar to that for a para-methyl substituent) suggest that para/meta ratios of ca. 15–20/1 should be observed for benzylation of 2,6-DMP, in contract to the observed ratio of ca. 1.6/1. In benzylation of 2,6-DMA the para/meta ratio should be about 7–8/1, in contrast to the observed 0.5/1 ratio. (These estimates ignore steric effects of ortho-methyl substituents, which should result in even greater discrepancies between observed and expected para/meta ratios.)

The conclusion that yields of meta-benzylation products from reactions of 2,6-DMP and 2,6-DMA are at least 10 times as great as expected is based on the assumption that meta-benzylation products are formed by direct substitution at the meta positions. Before this conclusion can be accepted, we must eliminate the possibility of formation of meta-benzylation products by more complex mechanisms.

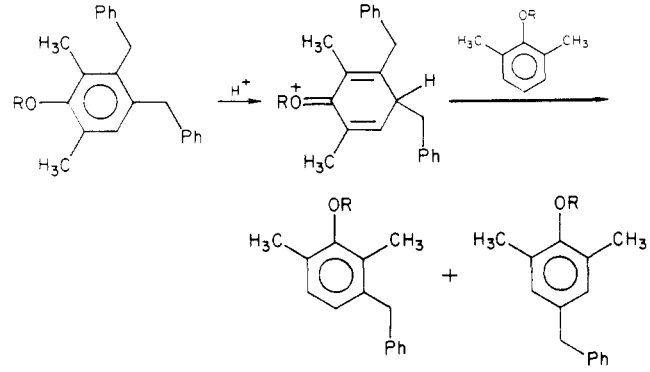
Distinguishing among Mechanisms for Meta Benzylation

Several possible mechanisms might account for the high percentage of meta substitution observed in benzylation of 2,6-DMP and 2,6-DMA.

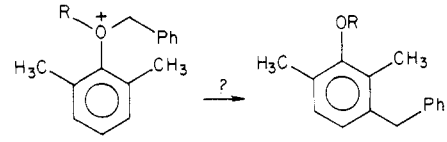
(a) Benzylation may occur predominantly at the para positions to yield **1** and **5**. These products might then rearrange under the acidic reaction conditions to form the meta-benzylated isomers **2** and **6**.



(b) Despite the presence of large excesses of 2,6-DMP and 2,6-DMA in the reaction mixtures, dibenzylation to form **3** and its methyl ether might occur to a significant extent. Preferential debenzylation at the para positions (presumably by reaction with 2,6-DMP or 2,6-DMA) might then yield **2** and **6**.

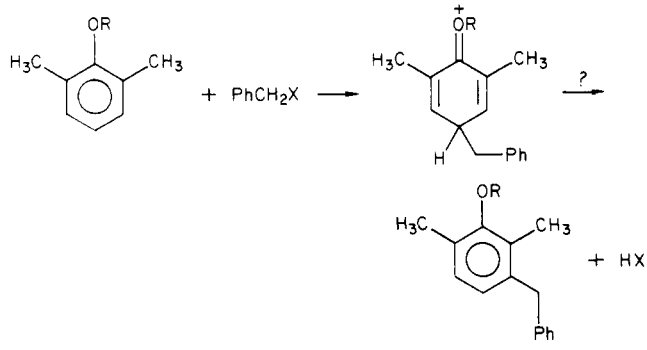


(c) Benzylation might initially occur at oxygen to yield benzyl 2,6-dimethylphenyl ether or its *O*-methyl oxonium salt. These products might then rearrange to form **2** and **6**.

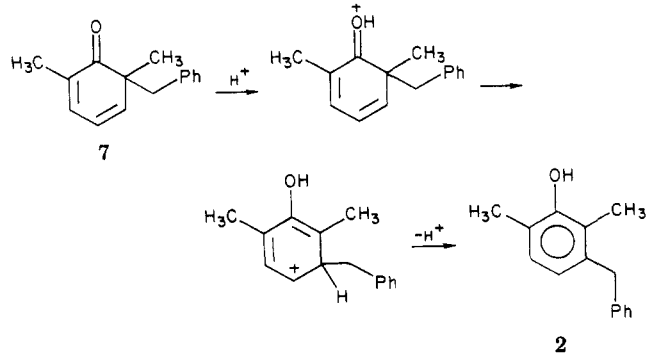


(d) Initial formation of benzyl 2,6-dimethylphenyl ether or its *O*-methyl oxonium salt might be followed by intermolecular transfer of benzyl groups to meta positions of 2,6-DMP or 2,6-DMA. (Since these are purely hypothetical mechanisms, we need not at present try to rationalize formation of meta benzylation products by mechanisms c or d.)

(e) The meta-benzylation products **2** and **6** might be formed by rapid rearrangement of the intermediate cations formed by benzylation of 2,6-DMP and 2,6-DMA at para positions.



(f) Benzylation might initially take place, in part, at ortho positions of 2,6-DMP or 2,6-DMA to form cyclohexadienone **7** or its *O*-methyl oxonium salt. 1,2-Migrations of the benzyl groups (catalyzed by acid in the case of the neutral ketone) would then give the observed meta-benzylation products.[7]



7 **2**

Table III. Benzylation of 2,6-Dimethylphenol-4-*d*[a] and 2,6-Dimethylanisole-4-*d*[b]

aromatic substrate	alkylating agent	catalyst/solvent	% meta isomer	% conversion
2,6-dimethylphenol-4-*d*	benzyl chloride	$ZnCl_2/CHCl_3$	36.4 ± 1.9	88
2,6-dimethylanisole-4-*d*	benzyl chloride	$ZnCl_2/CHCl_3$	68.7 ± 1.0	97
2,6-dimethylanisole-4-*d*	benzyl alcohol	$H_2SO_4/(C_2H_5)_2O$	73.9 ± 3.2	11

[a] Contains 0.94 atom of deuterium at C-4. [b] Contains 0.70 atom of deuterium at C-4.

(g) Benzylation might occur directly at meta positions, despite the normally much greater reactivity of para positions in phenols and aryl ethers.

The possibility that meta benzylation products might be formed by mechanism a could be easily eliminated. Phenol 1 was recovered unchanged after being heated in chloroform solution in the presence of zinc chloride and HCl or after being allowed to stand at room temperature in a solution of sulfuric acid in ether. Addition of 2,6-DMP to the solutions did not result in any change in the structures of 1. Phenol 2 was recovered unchanged from similar experiments.

The dibenzylphenol 3 was similarly recovered unchanged from treatment with the acid solutions employed for the Friedel-Crafts benzylations, either in the absence or presence of added 2,6-DMP. VPC analysis showed no evidence for formation of 1 or 2 in these reactions, eliminating the possibility that meta-benzylation products were formed by mechanism b.

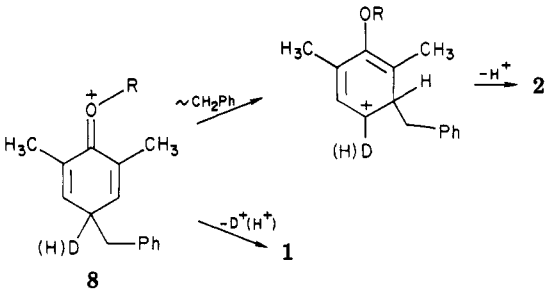
Benzyl 2,6-dimethylphenyl ether was recovered unchanged from a refluxing mixture of chloroform containing zinc chloride and HCl or from dilute solutions in ether containing sulfuric acid. When the ether was present in higher concentration in this solution, small amounts (ca. 3–10%) of unidentified products whose NMR spectra showed singlets in the δ 3–4 region were formed. The concentration effect showed that reaction was proceeding by intermolecular benzylation rather than by an intramolecular rearrangement as postulated in mechanism c. When a tenfold excess of 2,6-DMP was added to a solution of benzyl 2,6-dimethylphenyl ether in chloroform containing zinc chloride and HCl, no change occurred. However, reaction did take place in the ether–sulfuric acid solution to yield a mixutre of 1 and 2 as predicted by mechanism d. The meta-benzylation product 2 comprised 50.1 ± 2.8% of the product mixture. (The high percentage of meta benzylation is surprising, particularly in view of the large size of the 2,6-dimethylphenoxy leaving group, which might have been expected to favor reaction at the less hindered para position of 2,6-DMP.)

Although benzyl 2,6-dimethylphenyl ether can thus act as an alkylating agent in the presence of sulfuric acid, it was found to be a relatively unreactive one, since ca. 60% of the ether was recovered unchanged from reaction with a tenfold excess of 2,6-DMP. Thus, if any of the ether were formed during Friedel–Crafts benzylations, most of the ether would remain to be detected at the termination of the reaction. No benzyl 2,6-dimethylphenyl ether could be detected from reaction in chloroform–zinc chloride, but the sulfuric acid catalyzed reaction in ether with benzyl alcohol as the alkylating agent did result in formation of the ether amounting to ca. 10% of the combined yields of 1 and 2. Clearly, most of 2 formed in that reaction must have been formed without the intermediacy of benzyl 2,6-dimethylphenyl ether, but a small amount (up to 15%) may have been formed from reaction of 2,6-DMP with the ether. The fact that the percentage of meta-benzylation products formed with use of benzyl alcohol in ether–sulfuric acid is somewhat higher than those obtained with benzyl chloride as the alkylating agent may be due to partial intervention of mechanism d.

To test the possibility of benzyl group migrations in the σ-complexes resulting from para benzylation (mechanism e), we prepared 2,6-dimethylphenol-4-*d* by refluxing 2,6-DMP in alkaline deuterium oxide and 2,6-dimethylanisole-4-*d* was prepared by reaction of (3,5-dimethyl-4-methoxyphenyl)magnesium bromide with deuterium oxide. The deuterated phenol and anisole were subjected to Friedel–Crafts benzylations with benzyl chloride–zinc chloride in chloroform, and the anisole, in addition, was benzylated with benzyl alcohol in ether–sulfuric acid. The starting material recovered from each reaction was analyzed for deuterium content by NMR and, within experimental error, showed no exchange of hydrogen for deuterium in any reaction.

Comparison of the meta/para benzylation ratios from reaction of 2,6-DMP and 2,6-DMA (Tables I and II) with those from their deuterated analogues (Table III) demonstrates that the presence of a deuterium in place of a hydrogen atom at C-4 has no significant effect on the reactions of 2,6-DMP or 2,6-DMA.

If the meta-benzylation products were formed by mechanism e, the relative yields of meta- and para-benzylation products would depend on the rates of benzyl group migration vs. loss of a proton (or deuteron) at C-4 in the intermediate cation 8. Since the rates of formation of para-substituted products would be subject to a hydrogen isotope effect,[8] the absence of any detectable isotope effects on the product ratios are inconsistent with formation of meta-benzylation products by mechanism e.



Mechanism f seems perhaps the most plausible scheme for formation of meta-substituted phenols and aryl ethers by Friedel–Crafts benzylation. It has been demonstrated, for instance, that alumina-catalyzed methylation of 2,6-DMP to form 2,3,6-trimethylphenol at high temperatures proceeds by initial ortho methylation, followed by a 1,2-methyl migration.[9] In that reaction, however, it is presumably aluminum 2,6-dimethylphenoxide that is methylated rather than 2,6-DMP.

The most obvious (and frequently suggested) test of mechanism f would be to study the locations of labeled

(7) Miller, B. *Acc. Chem. Res.* **1975**, *8*, 245.

(8) A change in the ratio of meta to para substitution should be readily detected on deuterium substitution if mechanism e is operative, since a sizeable (≥4) hydrogen isotope effect should be observed: e.g., Zollinger, H. *Helv. Chim. Acta* **1955**, *38*, 1597, 1617; Grovenstein, E.; Kilby, D., *J. Am. Chem. Soc.* **1957**, *79*, 2972; Miller, B. *Ibid.* **1965**, *87*, 5111.

(9) Leach, B. E. *J. Org. Chem.* **1978**, *43*, 1794.

Table IV. Benzylation of Aromatic Ethers[a]

substrate	products % ortho	% meta	% para	% conversion
anisole	40.8 ± 0.4		59.2 ± 0.6	71
isopropyl phenyl ether	33.9 ± 0.2		66.1 ± 0.4	81
2,6-dimethylphenyl isopropyl ether		70.0 ± 1.0	30.0 ± 0.5	68
(phenol)	60.7 ± 0.6		39.3 ± 0.4	86

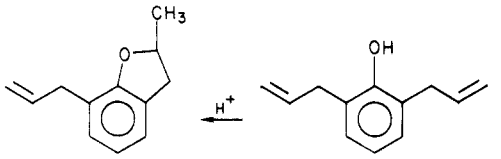
[a] All reactions were carried out with benzyl chloride in chloroform solution, employing $ZnCl_2$ as the catalyst.

benzyl groups in the products from reaction of 2,6-dibenzylphenol with isotopically labeled benzylating agents. However, our preliminary experiments have demonstrated that it would be extremely difficult to separate the components of the mixture of dibenzyl and tribenzylphenols obtained from the Friedel–Crafts reaction. We have therefore employed less direct methods of testing the validity of mechanism f.

If meta-benzylation products from 2,6-DMP and 2,6-DMA were obtained from initially formed ortho-benzylation products, the fact that benzylation of 2,6-DMA yields higher percentages of meta benzylation would suggest that ortho/para ratios from benzylation of anisoles should be higher than from benzylation of phenols. As can be seen from the data in Table IV, however, benzylation of anisole results in a higher percentage of para attack than does benzylation of phenol. This is presumably due principally to steric effects, as is the fact that replacing the methyl group on oxygen by an isopropyl group further decreases the ortho/para benzylation ratio.

In contrast, benzylation of 2,6-dimethylphenyl isopropyl ether yields essentially the same meta/para benzylation ratio as benzylation of 2,6-DMA. (NMR signals for the methine hydrogen of the benzylation products overlapped the signals for the diarylmethylene signlets, so that direct NMR analysis of the product ratios could not be obtained. Instead, the products were first cleaved to the corresponding phenols by reaction with refluxing hydriodic acid, and the meta/para ratios in the phenols established by NMR analysis. Studies with synthetic mixtures demonstrated that the cleavage reactions did not affect the meta/para ratio.) Comparison of the results summarized in Table IV with those in Tables I and II argue strongly against initial ortho benzylation in formation of meta-benzylation products.

A second test of the possibility that benzylation of 2,6-DMA occurs at ortho positions was carried out by taking advantage of the fact that acid-catalyzed migrations of allyl groups in linearly conjugated cyclohexadienones occur very rapidly via [3,3] migration processes.[7,10] Thus, if benzylation of 2,6-diallylphenol were to occur at an ortho position to yield cyclohexadienone **9**, rearrangement of **9** under the acidic reaction conditions should be expected to yield 2,4-diallyl-6-benzylphenol (**10**) rather than a product of benzyl migration. In fact, rearrangement of **9** (prepared by reaction of benzyl chloride with sodium 2,6-diallylphenoxide) in the presence of zinc chloride in chloroform did yield **10** as the sole product. Thus, if meta benzylation of phenols proceeds by iniital ortho attack, benzylation of 2,6-diallylphenol or its ethers should yield solely derivatives of 2,4-diallyl-6-benzylphenol and 2,6-diallyl-4-benzylphenol and no meta-benzylation products.



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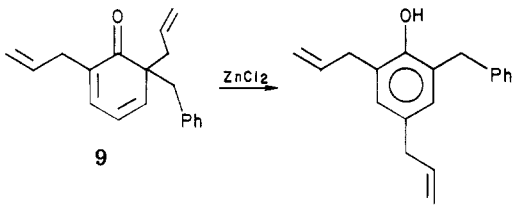
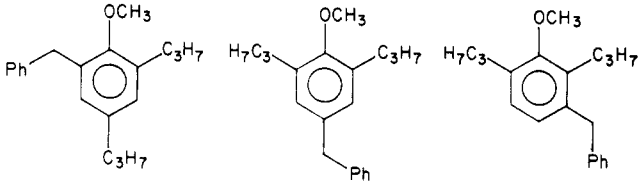


9 10

Unfortunately, attempts to benzylate diallylphenol under Friedel–Crafts conditions showed that cyclization to form chroman **11** occurred more rapidly than did benzylation. Therefore the Friedel–Crafts benzylation was carried out with 2,6-diallylanisole, whose cyclization to the chroman was a slower process. As with benzylation of 2,6-DMA, benzylation of 2,6-diallylanisole yielded an inseparable mixture of products. NMR analysis of the product mixture was difficult sine the diarylmethylene peaks were obscured by signals for the allylic methylene groups. However, hydrogenation of the product mixture gave a mixture of dipropylbenzylanisoles in which the diarylmethylene singlets were nicely separated from other peaks. To help identify the reaction products, we prepared independently the three possible products of benzylation and hydrogenation, 2-benzyl-4,6-dipropylanisole (**12**), 4-benzyl-2,6-dipropylanisole (**13**), and 3-benzyl-2,6-dipropylanisole (**14**). Although the diarylmethylene signals

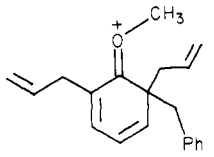


12 13 14

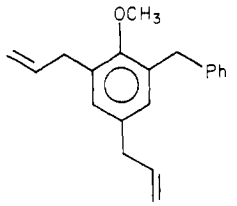
in the NMR spectra of the three isomers came at quite similar positions, addition of the NMR shift reagent Eu(fod)$_3$ to samples of each ether resulted in a somewhat greater downfield shift for the methylene singlet of the meta-benzyl isomer (**14**) than for the para-benzyl derivative **13**, while the shift per gram of added Eu(fod)$_3$ was nearly 4 times as large for the ortho-benzyl isomer **12** as for either of the others. Addition of weighed quantities of Eu(fod)$_3$ to the product from benzylation and hydrogenation of 2,6-diallylanisole resulted in separation of two diarylmethylene singlets, whose shifts per unit of Eu(fod)$_3$ corresponded to those of **13** and **14**. No peak corresponding to the ortho-benzylation product **12** could be detected.

As was mentioned above, cyclohexadienone **9** rearranges regiospecifically to **10** in acid. It would therefore be expected that **15**, the product of ortho benzylation of 2,6-diallylanisole, would yield the [3,3] rearrangement product **16** as the principal, if not the sole, rearrangement product. (The possibility that the presence of a methyl group, rather than a hydrogen, on the oxygen atom would seriously affect its mode of rearrangement seems unlikely, in view of the fact that a wide variety (e.g., acylation reagents, boron

(10) Miller, B. *J. Am. Chem. Soc.* **1970**, *92*, 6246.



15



16

trihalides) of reagents which attack oxygen catalyze [3,3] allyl shifts in linearly conjugated cyclohexadienones.[7] Taken together with the lack of steric effects expected for ortho benzylation, and the demonstration that allylation of 2,6-DMP and 2,6-DMA occurs directly at the meta position,[11] the absence of derivatives of **15** from benzylation of 2,6-diallylanisole provides convincing evidence that mechanism f is not the path leading to formation of meta-benzylation products from 2,6-disubstituted phenols and aryl ethers.

Since all other reasonable paths must be rejected, we conclude that meta benzylations of 2,6-disubstituted phenols and phenyl ethers proceed by direct electrophilic attack at the normally less reactive meta positions.

Experimental Section

Unless otherwise indicated, all reagents and solvents were Reagent Grade or were purified by standard methods before use. Anhydrous zinc chloride was prepared by fusing Analytical Grade Zinc chloride and storing the product in a desiccator until use.

All melting points and boiling points are uncorrected. NMR spectra were recovered on a Perkin-Elmer Model R12A spectrometer in deuteriochloroform solution, using Me_4Si as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 727 spectrometer. Vapor phase chromatographic separations were carried out on a 5% Apiezon L on Chromosorb W columns (5 ft × $^1/_8$ in. for analytical determinations and 5 ft × 0.25 in. for isolation of products).

4-Benzyl-2,6-dimethylphenol (1) was prepared by the procedure of v. Auwers and Janssen[12] as needles (from water), mp 67–67.5 °C (lit.[12] 66.5–66.7 °C). Its NMR spectrum showed singlets at δ 2.15 (6 H), 3.85 (2 H), 4.45 (1 H), and 6.75 (2 H, aromatic protons on phenolic ring), and a multiplet at δ 7.2 (5 H).

Synthesis of 3-Benzyl-2,6-dimethylphenol (2). a. 3-Benzyl-2,6-dimethylcyclohexanone. Benzylmagnesium chloride (prepared from 20.3 g (0.160 mol) of benzyl chloride and 3.55 g (0.146 mol) of magnesium turnings) was transferred through a glass-wool filter into a flask containing cuprous iodide (0.25 g, 0.0013 mol). The flask was cooled in ice and 2,6-dimethylcyclohex-2-en-1-one (10.5 g, 0.085 mol) was added, with stirring, over a 1.5-h period. A further 0.75 g of cuprous iodide was added in three portions during addition of the ketone. The mixture was stirred at room temperature for 18 h. Distilled water and dilute sulfuric acid were added, the resulting two-phase mixture was filtered, and the phases were separated. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under vacuum to yield 20.6 g of a viscous yellow oil. The product was subjected to steam distillation for a short period to give a distillate from which 6.3 g of bibenzyl could be obtained. The residue was extracted with methylene chloride and dried, the solvent evaporated, and the residue chromatographed on 150 g of neutral alumina (activity III), eluting with petroleum ether (30–60 °C) to yield 1.3 g of a product whose NMR and IR spectra indicated that it was a mixture of stereoisomers of 3-benzyl-2,6-dimethylcyclohexanone.

b. Chlorination and Dehydrochlorination of 3-Benzyl-2,6-dimethylcyclohexanone. The product obtained from the reaction above was dissolved in 5 mL of carbon tetrachloride and 3.0 g (6.0 mmol) of freshly distilled sulfuryl chlroide was added over the course of 5 min. The solution was stirred at room temperature for 3 h and then washed successively with distilled water, saturated aqueous sodium bicarbonate solution, and a saturated sodium chloride solution. The organic layer was dried over magnesium sulfate and filtered, and the solvent was removed under vacuum to yield 1.5 g of a yellow oil. In the NMR spectrum of the crude product the methyl doublets of the starting material were converted to singlets, indicating essentially complete conversion to 3-benzyl-2,6-dichloro-2,6-dimethylcyclohexanones.

The product was dissolved in *NN*-dimethylformamide (15 mL) and lithium chloride (1.0 g) was added. The mixture was stirred and heated on a steam bath for 24 h. It was then cooled to room temperature, and 60 mL of 4% aqueous sulfuric acid and 10 mL of dichloromethane were added. This mixture was stirred at room temperature for 24 h. The organic layer was separated, washed with saturated aqueous sodium bicarbonate, and dried over anhydrous sodium sulfate and the solvent was evaporated under vacuum to give 0.95 g of a brown oil.

The oil was dissolved in petroleum ether and extracted with Claisen's alkali, and the alkaline layer was reacidified with dilute hydrochloric acid and extracted with dichloromethane. The organic layer was washed with distilled water and dried over anhydrous sodium sulfate, and the solvent was evaporated under vacuum to give 0.17 g of a brown liquid, which crystallized on standing at room temperature for 2 months. Recrystallization from hexane gave white needles, mp 60–61 °C. Its NMR spectrum showed singlets at δ 2.0 and 2.1 (3 H each, methyl groups), 3.90 (2 H, diarylmethylene), and 4.65 (1 h, hydroxy), a doublet of doublets at δ 6.65 and 6.85 (J = 8 Hz, aromatic protons on phenolic ring), and a multiplet at δ 7.15 (5 H). Anal. Calcd for $C_{15}H_{16}O$: C, 84.86; H, 7.60. Found: C, 84.95; H, 7.66.

3-Benzyl-4-bromo-2,6-dimethylphenol. 3-Benzyl-2,6-dimethylphenol (0.51 g, 2.4 mmol) was dissolved in 5 mL of chloroform and cooled in an ice bath. A cold solution of bromine (0.38 g, 2.4 mmol) in 5 mL of chloroform was added dropwise. The solution was washed with aqueous sodium sulfite solution and then with distilled water and dried over sodium sulfate. Evaporation of the solvent under vacuum left 3-benzyl-4-bromo-2,6-dimethylphenol (0.70 g, 2.4 mmol, 100%) as a dark oil. Two recrystallizations from petroleum ether gave white crystals, mp 58–58.5 °C. Its NMR spectrum showed singlets at δ 2.10 and 2.20 (3 H each, methyl groups), 4.20 (2 H, methylene), and 4.6 (1 H, hydroxy) and a multiplet at 7.15 (6 H). Anal. Calcd for $C_{15}H_{15}BrO$: C, 61.66; H, 5.52. Found: C, 61.73; H, 5.70.

3-Benzyl-4-bromo-2,6-dimethylanisole. Potassium *tert*-butoxide (50 mg, 0.44 mmol) was added to a solution of 3-benzyl-4-bromo-2,6-dimethylphenol (0.12 g, 0.41 mmol) in 10 mL of dimethyl sulfoxide. Methyl iodide (3 mL) was added, and the mixture was shaken at room temperature for 5 min. It was then poured into water, the mixture was extracted with methylene chloride, and the methylene chloride solution was washed twice with water, once with Claisen's alkali, and again with water. The organic layer was dried over magnesium sulfate and filtered, and the solvent was evaporated to yield 0.11 g (36 mmol, 88%) of 3-benzyl-4-bromo-2,6-dimethylanisole as a pale yellow oil. Its NMR spectrum showed peaks at δ 2.15 (s, 3 H), 2.20 (s, 3 H), 4.22 (s, 2 H), and 6.8–7.2 (m, 6 H).

Electrophilic Benzylation of 2,6-Dimethylphenol. a. Reaction with Benzyl Chloride (1:1 Molar Ratio). A solution of 2,6-DMP (12.18 g, 0.100 mol) in 124 mL of chloroform was added to anhydrous zinc chloride (16.53 g, 0.121 mol). Benzyl chloride (13.2 g, 0.104 mol) was then added at once and the mixture was heated under reflux for 23 h.

The chloroform was evaporated under vacuum and the residual brown liquid subjected to steam distillation (2.5 L of distillate was collected). The material not distilled was extracted with carbon tetrachloride and dried over anhydrous sodium sulfate. The solvent was partially evaporated under vacuum, and the residue was then left in the hood. 2,6-Dimethyl-3,4-dibenzylphenol (2.81 g, 18%) precipitated as a white solid. Two recrystallizations from methanol gave 1.34 g (9%) of 3,4-dibenzyl-2,6-dimethylphenol as white crystals, mp 117–118.5 °C.

Its NMR spectrum showed peaks at δ 2.1 (s, 3 H, methyl), 2.2 (s, 3 H, methyl), 3.85 (s, 2 H, methylene), 4.0 (s, 2 H, methylene), 4.55 (s, 1 H, OH), and 6.8–7.4 (m, 11 H). Anal. Calcd for $C_{22}H_{22}O$:

(11) Miller, B.; McLaughlin, M. P. *Tetrahedron Lett.* **1978**, 3541.
(12) v. Auwers, K; Janssen, E. *Justus Liebigs. Ann. Chem.* **1930**, *483*, 55.

C, 87.37; H, 7.33. Found: C, 87.28; H, 7.30.

b. Reaction of Excess 2,6-Dimethylphenol with Benzyl Chloride ($ZnCl_2$ Catalysts). 2,6-DMP (11.9 g, 0.097 mol), benzyl chloride (1.10 g, 0.0087 mol), and anhydrous zinc chloride (1.22 g, 0.0090 mol) were added to 40 mL of chloroform and the mixture was heated at (68 °C) reflux for 15 h.

The reaction mixture was then cooled to room temperature and washed with distilled water, and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum and the residue was placed in a sublimer and kept at 48 °C and 29 torr for 33 h. The sublimate consisted solely of 2,6-dimethylphenol (NMR). The residue (4.73 g) consisted of approximately four-fifths 2,6-dimethylphenol and one-fifth benzylated phenol (NMR). (In later runs, the sublimation step was omitted.)

The NMR spectrum of the crude product showed two singlets at δ 3.75 and 3.85, the latter being the smaller peak (ca. 37%).

Sodium chloride (18 g) was added to this residue and the mixture subjected to steam distillation (2.5 L of distillate was collected). The residual liquid was seeded with a small crystal of 2,6-dimethyl-4-benzylphenol. After standing overnight, the mixture was filtered to yield 1.36 g (74%) of white crystals, mp 58.5–65 °C. (In later runs, the residue from steam distillation was extracted with methylene chloride, dried, and filtered and the solvent evaporated.) The NMR spectrum of the product corresponded to that of a mixture of 1 and 2 in the ratio 63:37.

When a sample of the crude product, before steam distillation, was analyzed by gas chromatography (240 °C, flow rate = 237 mL min^{-1}), two overlapping peaks appeared at retention times of 3.5 and 3.8 min, respectively. The NMR spectrum of a sample isolated by VPC was described above, with the minor product constituting 37.4 ± 3.1% of the total.

c. Reaction of Excess 2,6-Dimethylphenol with Benzyl Chloride Catalyzed by Calcium Chloride. Anhydrous calcium chloride (1.40 g, 0.013 mol) and benzyl chloride (0.99 g, 7.8 mmol) were added to a solution of 2,6-DMP (9.43 g, 0.0772 mol) in 30 mL of chloroform. The mixture was heated at reflux for 16 h, cooled, and washed 3 times with saturated sodium bicarbonate solution. The organic layer was dried over sodium sulfate and filtered and the solvent evaporated. Removal of unreacted 2,6-DMP by vacuum sublimination at 48 °C (25 torr) for 15 h gave a mixture of 1 and 2 containing 33% of 2.

d. Reaction in Nitromethane Catalyzed by Titanium Tetrachloride. Titanium tetrachloride (0.50 mL) was added to a solution of 2,6-DMP (7.50 g, 61.4 mmol) and benzyl chloride (0.71 g, 5.6 mmol) in 20 mL of nitromethane. The mixture was allowed to stand at room temperature for 2 h and then diluted with methylene chloride poured into a mixture of water and ice. The organic layer was washed 3 times with water, the solvent evaporated, and the residual material subjected to steam distillation. The undistilled material was worked up as usual to yield 0.82 g (3.86 mmol, 69%) of a mixture of 1 and 2.

e. Reaction of Excess 2,6-Dimethylphenol with Benzyl Alcohol in Diethyl Ether. Benzyl alcohol (1.05 g, 10 mmol) was added to a solution of 2,6-DMP (12.8 g, 0.105 mol) in 40 mL of diethyl ether. Concentrated sulfuric acid (10 mL) was then added dropwise over a 3-min period. After 2 h the mixture was poured into 200 mL of water, neutralized with sodium carbonate, and worked up as usual to yield 0.95 g (4.41 mmol, 44%) of a mixture of 1 and 2 as white crystals.

Bromination of the Product Mixture from the Reaction of Benzyl Chloride with Excess 2,6-Dimethylphenol. A portion (1.57 g, 7.39 mmol) of the product mixture from the zinc chloride catalyzed benzylation of 2,6-DMP carried out as described above, containing ca. 2.74 mmol of 2,6-dimethyl-3-benzylphenol, was dissolved in 10 mL of chloroform and cooled in ice. An ice-cold solution of bromine (0.48 g, 0.0030 mol) in 10 mL of chloroform was then added dropwise to the solution of phenols until it appeared that the reaction had ceased, whereupon aqueous sodium sulfite was immediately added and the mixture vigorously shaken.

The organic layer was washed with distilled water and dried over anhydrous sodium sulfate, and the solvent was evaporated under vacuum to yield 1.64 g of a clear orange liquid. The NMR spectrum of this liquid showed that the singlet formerly of δ 3.9 had disappeared, to be replaced by a singlet, with the same intensity, at δ 4.2. The singlet at δ 3.8, due to 2,6-dimethyl-4-benzylphenol, remained unchanged.

Gas chromatography (240 °C) showed peaks at retention times of 4.5 and 13.5 min. The component with a retention time of 13.5 min was collected and recrystallized 3 times from Skelly B to give 3-benzyl-4-bromo-2,6-dimethylphenol as white crystals, mp 58.5–59.5 °C.

2,6-Dimethylphenol-*4-d* was prepared by the procedure described for preparation of 2,6-dimethylphenol-*4-t*.[13] Its NMR spectrum showed the 3 H multiplet at δ 7.1–6.7 in the spectrum in 2,6-DMP converted to a singlet (2 H) at δ 6.95. NMR integration showed the product to contain 0.94 ± 0.02 atoms of deuterium at C-4.

Benzylation of 2,6-Dimethylphenol-*4-d*. Zinc chloride (1.8 g) was added to a solution of 2,6-dimethylphenol-*4-d* (2.15 g, 1.76 mmol) and benzyl chloride (0.33 g, 2.63 mol) in 15 mL of chloroform. After refluxing for 20 h, the reaction mixture was worked up as usual to yield 0.49 g (2.30 mmol) of a mixture of 1 and 2. Phenol 2 comprised 36.4 ± 1.9% of the mixture by NMR analysis. NMR analysis of 2,6-dimethylphenol-*4-d* recovered by steam distillation showed it to contain 0.95 ± 0.04 atoms of deuterium at C-4.

Electrophilic Benzylation of 2,6-Dimethylanisole. a. Reaction of 2,6-DMA with Benzyl Chloride Catalyzed by Zinc Chloride. Anhydrous zinc chloride (0.38 g, 0.0028 mol) and benzyl chloride (1.10 g, 0.0087 mol) were added to a solution of 2,6-DMA (10 .4 g, 0.0764 mol) in 30 mL of chloroform. The mixture was heated at reflux for 15 h and cooled, and the chloroform was evaporated under vacuum. The residue was extracted with petroleum ether–benzene (1:1), the organic layer was washed with water and sodium bicarbonate solution and dried over magnesium sulfate, and the solvent and excess 2,6-DMA were distilled off under vacuum. (In later runs, solvent and excess 2,6-DMA were removed by steam distillation.) A mixture of 5 and 6 was obtained as a yellow liquid. NMR analysis showed 6 to comprise 70.0 ± 2.6% of the total. A sample of the mixture was isolated by preparative gas chromatography (t_R 1.9 min at 240 °C). Its NMR spectrum was essentially identical with that of the crude product and showed 5 and 6 to be present in the ratio 30.5:69.5.

b. Reaction with Benzyl Alcohol Catalyzed by Sulfuric Acid. Benzyl alcohol (0.61 g, 5.6 mmol) was added to a solution of 2,6-DMA (7.61 g, 55.9 mmol) in 21 mL of diethyl ether. Concentrated sulfuric acid (5.2 mL) was added dropwise over a 1-min period. The mixture was kept at room temperature for 2 h and then poured into 50 mL of distilled water, and the ether layer was separated and neutralized with solid sodium carbonate. The reaction mixture was then worked up as usual to yield a mixture of 5 and 6.

c. Reaction with Benzyl Chloride Catalyzed by Titanium Tetrachloride. Titanium tetrachloride (0.50 g, 2.6 mmol) was added to a solution of 2,6-DMA (8.7 g, 79 mmol) and benzyl chloride (0.75 g, 5.9 mmol) in 30 mL of nitromethane. The solution was allowed to stand at room temperature for 2.5 h, poured into a mixture of ice and water, and extracted with methylene chloride. It was then worked up as usual to yield 1.13 g (86%) of a mixture of 5 and 6.

Bromination of the Product Mixture from Benzylation of 2,6-Dimethylanisole. A cold solution of bromine (0.84 g, 5.3 mmol) in 5 mL of chloroform was added to an ice-cooled solution containing 50 mL of chloroform and a portion (0.68 g) of the mixture of 5 and 6 obtained by zinc chloride catalyzed benzylation of 2,6-DMA. Addition of the bromine solution took 5 min. The reaction mixture was then shaken with sodium sulfite solution and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum leaving 0.6 g of bright yellow liquid. Its NMR spectrum showed the methylene peak of 6 at δ 3.9 to have disappeared to be replaced by a singlet at δ 4.15. VPC analysis at 240 °C showed peaks at $*_R$ 1.9 and 5.8 min. The components were isolated by preparative VPC and identified as 5 and **3-benzyl-4-bromo-2,6-dimethylanisole.**

Synthesis of 2,6-Dimethylanisole-*4-d*. (3,5-Dimethyl-4-methoxyphenyl)magnesium bromide was prepared from 2,6-di-

(13) Butte, W. A., Jr.; Price, C. C. *J. Am. Chem. Soc.* **1962**, *84*, 3567.

methyl-4-bromoanisole (23.2 g, 0.108 mol) and magnesium (2.75 g, 0.113 mol) in 400 mL of THF. Deuterium oxide (11.1 g, 0.56 mol) was added dropwise over 10 min, with stirring. Stirring was continued while the mixture was refluxed for an additional hour.

A slight excess of 3% aqueous sulfuric acid was added, the mixture was stirred briefly, and the organic layer was separated, washed with saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum to give 13 g of a yellow liquid.

Fractional distillation of this product yielded 2,6-dimethylanisole-4-*d* as a colorless liquid (8.75 g, 59%), bp 82.5–83 °C (24 torr). Its NMR spectrum showed singlets at δ 2.25 (6 H, methyls), 3.65 (3 H, methoxy), and 7.0 (2 H, hydrogens at C-3 and C-5).

Multiple integration indicated that the product had 69.5 ± 6.4 atom % deuterium at C-4.

Reaction of Excess 2,6-Dimethylanisole-4-*d* with Benzyl Chloride–Zinc Chloride. The procedure employed for the reaction of benzyl chloride with 2,6-DMA was followed exactly, using 2,6-diethylanisole-4-*d* (69.5 ± 6.4 atom % d; 8.69 g, 0.0633 mol), benzyl chloride (0.80 g, 0.0063 mol), and anhydrous zinc chloride (0.035 g, 0.0026 mol). The crude product, a yellow oil, contained 1.67 g (97%) of benzylated dimethylanisoles (NMR). The 3-benzyl derivative comprised 69.7 ± 1.0% of the total product.

The excess starting anisole was recovered by distillation during workup. Its NMR spectrum was unchanged, indicating the presence of 68.0 ± 5.0 atom % deuterium.

Reaction Excess 2,6-Dimethylanisole-4-*d* with Benzyl Alcohol Catalyzed by Sulfuric Acid. The procedure described for the reaction of 2,6-DMA with benzyl alcohol in the presence of sulfuric acid was followed, starting with 5.66 g of 2,6-dimethylanisole-4-*d*. The reaction was worked up as usual to yield 0.10 g (11%) of a mixture of deuterated **5** and **6**. A sample isolated by preparative gas chromatography contained 73.9 ± 3.2% of **6** by NMR analysis. The recovered 2,6-dimethylanisole contained 64.2 ± 8.3% deuterium (NMR).

2,6-Dimethylphenyl Propyl Ether. Anhydrous potassium carbonate (13.6 g, 0.0984 mol) and 1-bromopropane (12.2 g, 0.099 mol) were added to a solution of 2,6-DMP (12.0 g, 0.0982 mol) in 50 mL of acetone. The mixture was heated on a steam bath, with stirring, for 16 h. It was then cooled and a mixture of petroleum ether and benzene (1:1) was added. The solution was washed with water, with Claisen's alkali, and again with water. The organic layer was dried over magnesium sulfate and filtered, and the solvent was removed under vacuum. Fractional distillation gave **2,6-dimethylphenyl propyl ether** as a colorless liquid (7.35 g, 46%), bp 56–60 °C. Its NMR spectrum showed peaks at δ 1.05 (t, J = 7 Hz, 3 H), 1.75 (m, $J \sim 7$ Hz, 2 H), 2.20 (s, 6 H), 3.65 (t, J = 7 Hz, 2 H), and 6.9 (narrow m, 3 H).

2,6-Dimethylphenyl Hexyl Ether. Sodium hydroxide (1.27 g, 0.0318 mol) was added to a solution of 2,6-DMP (3.10 g, 0.0254 mol) in 15 mL of dimethyl sulfoxide. The mixture was heated at 100–110 °C for 1 h. 1-Chlorohexane (4.00 g, 33.2 mmol) was then added dropwise over a 15-min period. Heating was continued for 6 h. The reaction mixture was cooled, distilled water was added, and the solution was extracted with petroleum ether. The organic layer was washed with Claisen's alkali, then with water until the washings were neutral, and then dried over magnesium sulfate. The solvent was evaporated under vacuum to give a yellow oil, which was distilled twice under vacuum to give 2,6-dimethylphenyl hexyl ether (3.38 g, 65%) as a colorless liquid, bp 75–85 °C (1 torr). Its NMR spectrum showed peaks at δ 1.4 (br m, 1 H), 2.25 (s, 6 H), 3.73 (t, 2 H, J = 6 Hz), and 6.9 (m, 3 H).

Benzylation of Excess 2,6-Dimethylphenyl Propyl Ether. The reaction was carried out as described for the benzylation of dimethylanisole, starting with 2,6-dimethylphenyl propyl ether (7.35 g, 0.0448 mol), benzyl chloride (0.66 g, 0.0052 mol), and anhydrous zinc chloride (0.76 g, 0.0056 mol).

Workup as usual gave a yellow oil containing 0.97 g (73%) of benzylated 2,6-dimethylphenyl propyl ethers (NMR). A sample of the product mixture was isolated by preparative gas chromatography (t_R 6.5 min at 250 °C). Its NMR spectrum showed peaks at δ 1.05 (m, 3 H), 2.15, 2.20, and 2.25 (singlets totalling 6 H), 1.5–2.05 (m, 2 H), 3.5–3.9 (m, 2 H), 3.85 and 3.95 (singlets totalling 2 H), and 6.8–7.4 (m, 7 H).

2,6-Dimethyl-3-benzylphenyl propyl ether was estimated to comprise 79% of the product mixture (NMR analysis). However, the *O*-methylene absorptions slightly overlapped the diarylmethylene peaks, resulting in a less reliable product analysis than for benzylation of 2,6-DMA.

Benzylation of 2,6-Dimethylphenyl Hexyl Ether. Benzylation was carried out as described above, employing 2,6-dimethylphenyl hexyl ether (3.40 g, 0.0165 mol), benzyl chloride (0.275 g, 0.0022 mol), and anhydrous zinc chloride (0.48 g, 0.0035 mol). The reaction was worked up as usual to yield a mixture of benzylated ethers as a yellow oil (0.42 g, 66%). Its NMR spectrum showed peaks at δ 0.7–1.95 (m, 11 H), 2.15, 2.20, and 2.25 (singlets totalling 6 H), 3.8 and 3.9 (singlets totalling 2 H), 3.5–3.9 (m, 2 H), and 6.7–7.4 (m, 7 H). The NMR spectrum showed the component with the singlet at δ 3.9 to be the major component, but precise analysis was again impossible.

Bromine (0.16 g, 0.98 mmol) was added to a solution containing a portion (0.42 g, 1.4 mmol) of the product mixture. The reaction was worked up as described for bromination of the products from benzylation of 2,6-DMA. In the NMR spectrum of the crude bromination product the singlet at δ 3.9 had disappeared and was replaced by a singlet at δ 4.15. NMR integration suggested that the component with the singlet at δ 4.15 comprised approximately 65% of the total.

2,6-Dimethylphenyl benzyl ether was prepared as described for the synthesis of 2,6-dimethylphenyl propyl ether, starting with 5.11 g (0.0418 mol) of 2,6-DMA and 5.5 g (0.043 mol) of benzyl chloride. After workup as described above, the crude reaction product was subjected to steam distillation. The undistilled material was extracted with methylene chloride, dried over magnesium sulfate, and filtered, and the solvent was evaporated under vacuum to yield 2,6-dimethylphenyl benzyl ether (3.98 g, 48%) as a pale yellow oil, which showed a single component on VPC analysis. Its NMR spectrum showed peaks at δ 2.25 (s, 6 H), 2.75 (s, 2 H), and 7.0–7.65 (m, 8 H).

2,6-Dimethylphenyl Isopropyl Ether. Anhydrous potassium carbonate (44.2 g, 0.32 mol) was added to a solution of 2,6-dimethylphenol (37.3 g, 0.305 mol) in 100 mL of acetone and the mixture was heated under reflux for 30 min. A solution of isopropyl bromide (49.2 g, 0.40 mol) in 50 mL of acetone was added and heating was continued for 18.5 h. The reaction mixture was poured into water, the mixture extracted with petroleum ether, and the organic layer washed with Claisen's alkali and then with water. The petroleum ether solution was dried over magnesium sulfate and filtered, the solvent evaporated, and the residual liquid distilled to yield 11.75 g (0.072 mol, 24%) of 2,6-dimethylphenyl isopropyl ether, bp 42.5–43.0 °C (5 torr). Its NMR spectrum showed peaks at δ 6.95 (s, 3 H), 4.15 (h, 1 H, Js = 6.7 Hz), 2.25 (s, 6 H), 1.25 (d, 6 H, J = 6.7 Hz). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.14; H, 9.52.

2-Benzylphenyl Isopropyl Ether. The reaction between 2-benzylphenol and isopropyl chloride was carried out on a 5-mmol scale as described for the preparation of 2,6-dimethylphenyl isopropyl ether to yield 10.7 g (4.7 mmol, 94%) of the ether as a colorless oil. Its NMR spectrum showed peaks at δ 7.20 (s, 5 H), 7.18–6.70 (m, 4 H), 4.48 (h, J = 6.7 Hz, 1 H), 3.95 (s, 2 H), 1.23 (d, J = 6.7 Hz, 6 H). Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.66; H, 8.04.

4-Benzylphenyl isopropyl ether was prepared from 4-benzylphenol in 97% yield on a 5-mmol scale as described above. It was obtained a colorless liquid, bp 103–104 °C (0.4 torr) [lit.[14] 102 °C (0.2 torr)]. Its NMR spectrum showed peaks at δ 7.15 (s, 5 H), 7.04 (d, J = 8.7 Hz, 2 H), 6.74 (d, J = 8.7 Hz, 2 H), 4.40 (h, J = 6.7 Hz, 1 H), 3.85 (s, 3 H), and 1.23 (d, J = 6.7 Hz, 6 H).

Benzylation of 2,6-Dimethylphenyl Isopropyl Ether. 2,6-Dimethylphenyl isopropyl ether (6.67 g, 0.041 mol) was reacted with benzyl chloride (1.5 mmol) in chloroform in the presence of zinc chloride for 16 h as described for the benzylation of 2,6-dimethylanisole. The reaction product was subjected to vacuum distillation to remove the starting ether, and the residue was dissolved in 50 mL of petroleum ether and extracted with three 15-mL portions of Claisen's alkali. The alkali soluble fraction

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was acidified with HCl, extracted with petroleum ether, and dried, and the solvent was evaporated to yield 0.18 g of a mixture of 3-benzyl- and 4-benzyl-2,6-dimethylphenol. The alkali-insoluble material was washed with distilled water and dried over magnesium sulfate, and the solvent was evaporated to yield 0.8 g of a mixture of 3-benzyl- and 4-benzyl-2,6-dimethylphenyl isopropyl ethers. This mixture was added to 5 mL of HI and heated under reflux for 5 h. Distilled water was then added and isopropyl iodide removed by steam distillation. The residue was cooled, extracted with methylene chloride, washed with sodium bicarbonate solution, and dried, and the solvent was evaporated to yield a mixture of 3-benzyl- and 4-benzyl-2,6-dimethylphenols, whose composition was determined by NMR analysis.

2,6-Diallyl-6-benzylcyclohexa-2,4-dien-1-one. 2,6-Diallylphenol (7.3 g, 0.042 mol) was added to a solution of sodium hydroxide (1.65 g, 0.041 mol) in 35 mL of distilled water. This mixture was heated in an oil bath at 60 °C for 45 min. Benzyl bromide (7.2 g, 0.072 mol) was then added dropwise over 4 min. The resulting mixture was heated, with stirring, for 1 h. The oil bath was then removed and the stirring was continued for an additional hour.

The reaction mixture was poured into 30 mL of distilled water and the solution extracted with 40 mL of petroleum ether. The organic layer was washed with two 10-mL portions of Claisen's alkali and then with saturated aqueous sodium chloride until the washings were neutral. The solution was dried over anhydrous magnesium sulfate, and the solvent was evaporated under vacuum to yield a yellow oil, which was chromatographed on alumina, eluting with petroleum ether–methylene chloride (10:1). The dienone was obtained as a bright yellow oil (0.47 g., 4.2%): λ_{max} 324 nm (log ϵ 3.69); μ_{max} 1655, 1645. Its NMR spectrum showed a pair of doublets (J = 13 Hz) at δ 2.75 and 3.02 (totalling 2 H, benzylic methylene protons) superimposed on a multiplet for the allylic methylene group at C-6. Anal. Calcd. for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.10; H, 7.71.

Rearrangement of 2,6-Diallyl-6-benzylcyclohexa-2,4-dien-1-one in the Presence of Zinc Chloride. A solution of 2,6-diallyl-6-benzylcyclohexa-2,4-dien-1-one (0.16 g, 0.61 mmol) in 10 mL of chloroform was added to anhydrous zinc chloride (0.10 g, 0.74 mmol). This mixture was stirred at room temperature for 80 min and then washed with 20 mL of distilled water. The chloroform was evaporated under vacuum and the residue dissolved in petroleum ether and extracted with two 5-mL portions of Claisen's alkali. The alkaline extract was reacidified with dilute hydrochloric acid and then brought to approximatley neutral pH with solid potassium bicarbonate. The resulting mixture was extracted with methylene chloride and the organic layer was separated and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum to give 0.030 g (19%) of a brown oil.

The NMR and IR spectra of the product were identical with those of 2,4-diallyl-6-benzylphenol. There was a clean singlet at δ 6.83 in the NMR spectrum, indicating that [1,2] migration of either the benzyl or allyl groups did not take place.

4-Benzyl-2,6-diallylanisole. Anhydrous potassium carbonate (25.0 g, 0.181 mol) and allyl bromide (21.7 g, 0.179 mol) were added to a solution of 4-benzylphenol (30.0 g, 0.163 mol) in 100 mL of acetone. The mixture was stirred and heated on a steam bath for 16 h. The reaction mixture was cooled and a mixture of petroleum ether and benzene (1:1) added. The resulting mixture was washed with water, with Claisen's alkali, and again with water until the aqueous washings were neutral. The organic layer was dried over magnesium sulfate and filtered, and the solvent was removed under vacuum to yield 33.9 g of allyl 4-benzylphenyl ether as a viscous yellow oil. The oil was dissolved in 20 g of *N,N*-dimethylaniline and the solution heated in an oil bath at 240 °C for 75 min. The solution was then cooled and diluted with petroleum–ether benzene 1:1), and the solution was extracted with 10% hydrochloric acid. The organic layer was extracted with Claisen's alkali and the alkaline layer reacidified with dilute hydrochloric acid. The phenol thus generated was dissolved in petroleum ether–benzene (1:1). The solution was washed with water and dried over anhydrous sodium sulfate and filtered, and the solvent was removed under vacuum to yield 31.6 g of 2-allyl-4-benzylphenol as a brown liquid. The product was converted to its allyl ether as described above for allylation of 4-benzylphenol, and the ether was subjected to Claisen rearrangement in *N,N*-dimethylaniline as previously described to yield 25.9 g of 2,6-diallyl-4-benzylphenol as a brown liquid. The product was dissolved in 100 mL of acetone, and anhydrous potassium carbonate (14.1 g, 0.102 mol) and iodomethane (15 g, 0.105 mol) were added. The mixture was stirred and heated on a steam bath for 16 h. Additional iodomethane (9.1 g, 0.064 mol) was then added, and refluxing was continued for 6 h. The reaction mixture was cooled, diluted with petroleum ether–benzene, and washed with water. The organic layer was extracted with Claisen's alkali, washed with water, dried over magnesium sulfate, and filtered, and the solvent was removed under vacuum to yield 4-benzyl-2,6-diallylanisole (17.9 g, 40%) as a yellow liquid. An analytical sample was obtained by preparative gas chromatography (t_R 5.2 min at 240 °C). Its NMR spectrum showed peaks at δ 3.4 (m, 4 H, allylic methylene), 3.65 (S, 3 H, *O*-methyl), 3.85 (S, 2 H, diarylmethylene), 4.85–5.25 (m, 4 H, terminal vinyl protons), 5.65–6.40 (m, 2 H, secondary vinyl protons), 6.85 (s, 2 H, protons at C-3 and C-5), and 7.15 (narrow m, 5 H, phenyl group). Anal. Calcd for $C_{20}H_{22}O$: C, 86.29; H, 7.97. Found: C, 86.13; H, 7.28.

4-Benzyl-2,6-dipropylanisole. Palladium on charcoal (5%, 0.02 g) was added to a solution of 4-benzyl-2,6-diallylanisole in 30 mL of methanol. The mixture was stirred under hydrogen at a pressure of 1 atm until hydrogen absorption ceased (5.5 h). It was filtered twice and the solvent removed under vacuum to yield 4-benzyl-2,6-dipropylanisole as a pale yellow oil (0.28 g, 69%). Its NMR spectrum showed no vinyl absorptions. A purified sample was obtained by preparative gas chromatography (t_R 4.6 min at 240 °C). Its NMR spectrum showed peaks at δ 0.90 (t, J = 8 Hz, 6 H), 1.55 (m, 4 H), 2.50 (t, J = 7 Hz, 4 H), 3.85 (s, 2 H), 6.85 (s, 2 H, and 7.2 (narrow m, 5 H).

3-Benzyl-2,6-diallylanisole was prepared in 5% overall yield by a series of Claisen rearrangements as described for the synthesis of 4-benzyl-2,6-diallylanisole, starting with 5.0 g of 3-benzylphenol. An analytical sample was obtained by preparative gas chromatography t_R 5.6 min at 240 °C). Its NMR spectrum showed peaks at ca. δ 3.4 (m, 4 H), 3.70 (s, 3 H), 3.95 (s, 2 H), 4.65–5.3 (m, 4 H), 5.6–6.4 (m, 2 H), 6.8 (d, J = 7.8 Hz, 1 H), 6.93 (d, J = 7.8 Hz, 1 H), and 7.15 (m, 5 H). Anal. Calcd for $C_{20}H_{22}O$: C, 86.29; H, 7.97. Found: C, 85.87; H, 8.19.

3-Benzyl-2,6-dipropylanisole was prepared by hydrogenation of 3-benzyl-2,6-diallylanisole and purified by preparative gas chromatography. Its NMR spectrum showed peaks at ca. δ 0.9 (m, 6 H), 1.5 (m, 4 H), 2.55 (m, 4 H), 3.7 (s, 3 H), 3.95 (s, 2 H), 6.80 (d, J = 8.1 Hz, 1 H), 6.96 (d, J. = 8.1 Hz, 1 H), and 7.15 (m, 5 H).

2-Benzyl-4,6-diallylanisole was prepared in 30% overall yield by the same sequence of reactions employed for synthesis of 4-benzyl-2,6-diallylanisole, starting with 10.7 g of 2-benzylphenol. A sample was purified by preparative gas chromatography (t_R 4.9 min at 240 °C). Its NMR spectrum showed signals at ca. δ 3.35 (m, 4 H), 3.60 (s, 3 H), 4.0 (s, 2 H), 5.0 (m, 4 H), 5.5–6.4 (m, 2 H), 6.77 (d, J = 7.3 Hz, 1 H), 6.92 (d, J = 7.3 Hz, 1 H), and 7.2 (m, 5 H). Anal. Calcd for $C_{20}H_{22}O$: C, 86.29; H, 7.97. Found: C, 86.41; H, 8.10.

2-Benzyl-4,6-dipropylanisole was prepared by hydrogenation of 2-benzyl-4,6-diallylanisole and purified by preparative gas chromatography. Its NMR spectrum showed peaks at ca. δ 0.9 (m, 6 H), 1.55 (m, 4 H), 2.6 (m, 4 H), 3.6 (s, 3 H), 4.0 (s, 2 H), 6.9 (dd, J = 7.2 Hz, 2 H), and 7.2 (m, 5 H).

Reaction of 2,6-Diallylanisole with Benzyl Chloride–Zinc Chloride. A solution of 2,6-diallylanisole (9.9 g, 0.053 mol) in 30 mL of chloroform was added to anhydrous zinc chloride (0.83 g, 0.0061 mol). Benzyl chloride (0.66 g, 0.0052 mol) was added and the mixture was heated at reflux for 16.5 h. It was worked up as usual by steam distillation to yield 0.81 g of yellow oil. A portion of this product (0.42 g) was chromatographed on neutral alumina (activity III) to yield 0.22 g of product apparently still containing some material resulting from addition of HCl to alkene groups. This product was rechromatographed to yield 0.044 g of material whose NMR and IR spectra indicated the presence only of benzyldiallylanisoles. The mixture was dissolved in 10 mL of methanol, Pd on C (0.005 g) was added, and the mixture was stirred under a hydrogen atmosphere until hydrogen absorption ceased. It was then filtered, and the solvent was removed under vacuum to yield 0.04 g of a mixture of 4-benzyl-2,6-di-

propylanisole and 3-benzyl-2,6-dipropylanisole as a colorless oil.

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Registry No. 1, 41772-31-0; 2, 31040-78-5; 2-4-*d*, 80227-74-3; 3, 80227-75-4; 4, 80227-76-5; 5, 61259-78-7; 6, 69804-73-5; 6-4-*d*, 6-4-*d*; 9, 80227-78-7; 10, 80227-79-8; 12, 80227-80-1; 13, 80227-81-2; 14, 80227-82-3; 16, 80227-83-4; benzyl chloride, 100-44-7; 2,6-dimethylcyclohex-2-en-1-one, 40790-56-5; 3-benzyl-2,6-dimethylcyclohexanone, 80227-84-5; 3-benzyl-2,6-dichloro-2,6-dimethylcyclohexanone, 80227-85-6; 3-benzyl-4-bromo-2,6-dimethylanisole, 80227-86-7; 2,6-dimethylphenol, 25134-01-4; benzyl alcohol, 100-51-6; 2,6-dimethylphenol-4-*d*, 22100-63-6; 2,6-dimethylanisole, 1004-66-6; 2,6-dimethyl-4-bromoanisole, 14804-38-7; 2,6-dimethylanisole-4-*d*, 80227-87-8; 2,6-dimethylphenyl propyl ether, 61144-80-7; 2,6-dimethylphenyl hexyl ether, 80227-88-9; 2,6-dimethyl-4-benzylphenyl propyl ether, 80242-66-6; 2,6-dimethyl-3-benzylphenyl propyl ether, 80242-67-7; 3-benzyl-2,6-dimethylphenyl hexyl ether, 80227-89-0; 4-benzyl-2,6-dimethylphenyl hexyl ether, 80227-90-3; 3-benzyl-4-bromo-2,6-dimethylphenyl hexyl ether, 80227-91-4; 2,6-dimethylphenyl benzyl ether, 19578-74-6; 2,6-dimethylphenyl isopropyl ether, 54350-31-1; 2-benzylphenyl isopropyl ether, 80227-92-5; 2-benzylphenol, 534-83-8; 4-benzylphenyl isopropyl ether, 35672-53-8; 4-benzylphenol, 101-53-1; 3-benzyl-2,6-dimethylphenyl isopropyl ether, 69804-74-6; 4-benzyl-2,6-dimethylphenyl isopropyl ether, 80227-93-6; 2,6-diallylphenol, 3382-99-8; allyl 4-benzylphenyl ether, 22857-99-4; 2-allyl-4-benzylphenol, 80227-94-7; 2,6-diallyl-4-benzylphenol, 80227-95-8; 4-benzyl-2,6-diallylanisole, 80227-96-9; 3-benzyl-2,6-diallylanisole, 80227-97-0; 3-benzylphenol, 22272-48-6; 2,6-diallylanisole, 55980-23-9; anisole, 100-66-3; 2-benzylanisole, 883-90-9; 4-benzylanisole, 834-14-0; isopropyl phenyl ether, 2741-16-4; phenol, 108-95-2.

(*E*)-5-Hydroxypyrrolizidin-3-one: Versatile Synthon for the Synthesis of 5-Substituted 2-Pyrrolidones and (*Z*)-3-Alkylpyrrolizidines

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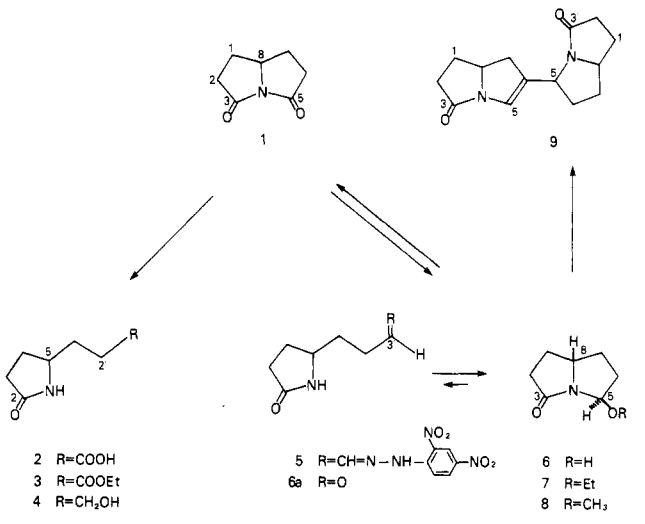
Carbinol lactam **6** of secured stereochemistry served as a synthon to prepare 5-substituted 2-pyrrolidones and pyrrolizidin-3-ones. The relative stereochemistry of **6** and the dithioketal **13**, prepared from the keto lactam **11**, was established by single-crystal X-ray analysis. Desulfurization of the dithioketals **13** and **14** afforded the 5-*n*-propylpyrrolizidin-3-ones **15** and **16**. Reduction of lactam **15** with $LiAlH_4$ gave the racemic (*Z*)-3-*n*-propylpyrrolizidine (**17**), an analogue of a substance recently detected in ant species.

The dioxopyrrolizidine **1**, prepared by Šorm et al.[1] and Micheel et al.[2,3] from γ-oxopimelic acid, is an attractive substance for preparing 5-substituted 2-pyrrolidones and 3- and 3,5-substituted pyrrolizidines. Representatives of the latter group of compounds have been described by several investigators[4] and recently have been found to occur in nature.[5] We now report a successful conversion of **1** into 5-(3-hydroxypropyl)-2-pyrrolidone (**4**) and an almost stereocontrolled synthesis of (±)-(*Z*)-3-*n*-propylpyrrolizidine (**17**), a close analogue of a natural ant toxin.[5]

The strained dilactam **1** reacted smoothly with ethanol in the presence of catalytic amounts of acid or base to give the ester **3** in 96% yield (Scheme I). Reduction of **1** with LAH in THF at room temperature gave the crystalline carbinol lactam **6** in 30% yield. Oxidation of **6** with Jones reagent regenerated the dilactam **1**. The structure of **6** was also in agreement with its spectral data, showing multiplets for C_8 H at δ 4.14. The relative stereochemistry present in **6** (C_5 H to C_8 H) could, however, not be solved unambiguously, and this point was determined by a single-crystal X-ray analysis. These data showed that the carbinol lactam **6** had the *E* configuration (C_5 H trans to C_8 H) and are summarized below (Figure 1).

Scheme I



Carbinol lactam **6** in solution is in equilibrium with the tautomeric aldehyde **6a** and the reaction products obtained can be correlated with this tautomerism.[6] The formation of a crystalline dinitrophenylhydrazone, **5**, and the re-

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