as shown by the fact that the compound gave a positive test with 2,4-dinitrophenylhydrazine reagent.

Attempts to Form Host Collared Diazo Compounds. Treatment of *p*-methylbenzenediazonium tetrafluoroborate (**16**) complexed 1:1 with cycle **12** in CH_2Cl_2 at −75 °C with the following reagents gave the following products: *p*-tolyllithium in ether gave six products (TLC), only *p*-$CH_3C_6H_4N_2C_6H_4CH_3$-*p* (4%) being identified; *N,N*-dimethylaniline in CH_2Cl_2 gave (85%) *p*-$CH_3C_6H_4N_2C_6H_4N(CH_3)_2$-*p*. Di-*p*-tolylzinc in ether–tetrahydrofuran added to a solution at −10 °C of 1:1 **16** and 18-crown-6 in CH_2Cl_2 gave 40% *p*-$CH_3C_6H_4N_2C_6H_4CH_3$-*p* and about five other products. Similar results were obtained with *p*-chloro- and *p*-methoxybenzenediazonium salts. No evidence of host-collared diazo compounds could be detected among any of these products using ^1H NMR and chromatographic behavior as criteria.

References and Notes

(1) (a) This work was supported by a grant from the National Science Foundation, GP-33533X, and by the U.S. Public Health Service, Research Grant No. GM12640-12 from the Department of Health, Education, and Welfare. (b) National Science Foundation Predoctoral Fellowship, 1972–1975.
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(20) We warmly thank Dr. G. D. Y. Sogah for this preparation.
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Intramolecular Oxidative Coupling of Diphenolic, Monophenolic, and Nonphenolic Substrates

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Abstract: A series of diphenolic, monophenolic, and nonphenolic 1,3-diarylpropanes were used as model substrates in a search for efficient new methods for intramolecular oxidative coupling. Vanadium oxytrichloride was found to be an effective oxidant for all three types of substrate under appropriate conditions. Thallium(III) trifluoroacetate and silver(II) trifluoroacetate gave good yields of monophenolic coupling.

It has long been recognized that an intramolecular oxidative phenol coupling reaction (Scheme I) serves as the key step in the biosynthesis of many classes of natural products,[1] and that the nonenzymic analogue of this transformation can lead to elegantly simple laboratory syntheses of these compounds.[2] However, full realization of this synthetic potential has been limited by the low yields usually encountered when the coupling step is carried out in the laboratory.[3] The major problems associated with making this approach synthetically useful are (1) generating the electron-deficient intermediate (Scheme I) under conditions that minimize polymerization resulting from intermolecular coupling of either the substrate or the intramolecularly coupled product, and (2) controlling the sites

Scheme I

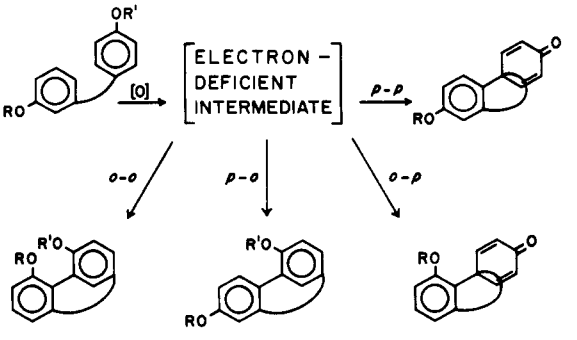


Table I. Oxidative Coupling of Diphenol **1** with Various Reagents

Oxidant	Solvent	Temp, °C	Yield,[a] % 7	Yield,[a] % 1
$K_3Fe(CN)_6$/ Na_2CO_3	$H_2O/CHCl_3$	25	4	*b*
$FeCl_3$	H_2O/t-BuOH	50	3[c]	66[c]
$AgNO_3/NaH$	CH_3CN/Et_2O	−60; 80	0	16
Ag_2CO_3-Celite[d]	C_6H_6	80	2	72
$Mn(acac)_3$[e]	CH_3CN	81	10[c]	16[c]
$MoOCl_4$[f]	CCl_4/Et_2O	−30; 25	18	26
Pt anode	H_2O/CH_3CN[g]	25	2.5	5

[a] Yield of isolated material, homogeneous to TLC analysis, unless otherwise specified. [b] Yield not determined. [c] Determined by gas chromatographic analysis of the trimethylsilylated reaction mixture, using an internal standard. [d] Reference 30. [e] Reference 31. [f] Reference 32. [g] Containing NaOH and $NaClO_4$.

Table II. Thermal Decomposition of Bis(*tert*-butylperoxycarbonate) Derivative **8**[a]

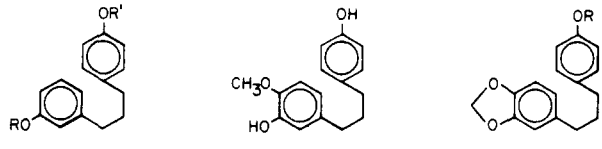
Solvent	Yield,[b] % Dienone 7	Yield,[b] % Diphenol 1
Benzene	4	41
Toluene	2.5	30
Cumene	3	55
Acetone	0	30
Acetonitrile	0	43
2-Propanol	0	95
Carbon tetrachloride	0	0[c]

[a] All reactions were carried out in anhydrous solvent in degassed sealed tubes at 125 °C for 4 h; initial concentration of **8** was 2.2×10^{-3} M. [b] Determined by gas chromatographic analysis of the trimethylsilylated reaction mixture, using an internal standard. [c] The product consisted entirely of highly insoluble polymeric material.

of bond formation on the aromatic rings to give the product of desired structural type and substitution pattern. Our efforts to solve the first of these problems are described in this paper,[4] while a solution to the second is still under active investigation in our laboratory.

The nature of the necessary electron-deficient intermediate (Scheme I) depends on the type of substrate being utilized. In the case of diphenolic substrates (R = R^1 = H), which are almost invariably involved in the biosynthetic process[3d] and which also had been exclusively used in the in vitro syntheses prior to our work,[4b] the required intermediate has been assumed to be a diphenoxy diradical (there have been some recent suggestions[3h] and evidence[5] to the contrary in certain cases, however). Monophenolic substrates (R = alkyl, R^1 = H) have been shown not to undergo intramolecular coupling when a phenoxy radical intermediate is generated;[6] the desired coupling reaction in this case presumably requires a more electrophilic phenoxy cation or cation radical (protonated phenoxy radical). Finally, oxidative coupling of nonphenolic substrates (R = R^1 = alkyl) of necessity requires cation radical intermediates. With these considerations in mind, we utilized a series of simple diphenolic, monophenolic, and nonphenolic 1,3-diarylpropanes as model substrates for the development of new synthetically useful chemical methods for intramolecular oxidative coupling.[4,7]

The diarylpropanes **1–6** were prepared from the appropriate



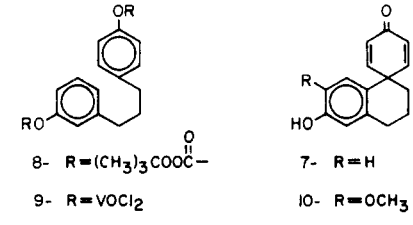
1- R=R'=H
2- R=H, R'=CH_3
3- R=R'=CH_3
4
5- R=H
6- R=CH_3

chalcones by catalytic hydrogenation–hydrogenolysis, followed by demethylation when necessary. Full details are given in the Experimental Section.

Diphenolic Coupling. Previous methods for intramolecular oxidative coupling of diphenols had been based almost exclusively on interaction of the substrate with a one-electron oxidant such as $K_3Fe(CN)_6$, $FeCl_3$, MnO_2, or Ag_2O.[3] Under these conditions the polymerization problem seemed to us to be insuperable, because high concentration with respect to the oxidant was needed in order to generate the supposed diradical intermediate, but high dilution with respect to the substrate was required to prevent intermolecular coupling; overoxidation of the phenolic products was also probable. We sought to circumvent this situation by finding an oxidant that could be covalently bonded to the substrate in stoichiometric amount prior to actual oxidation; the resulting intermediate (Scheme I, R = R^1 = oxidant) could then be induced to undergo homolytic cleavage (electron transfer) under high dilution, in the absence of excess oxidant.

Initial studies were carried out using diphenol **1**; the expected para–para coupled dienone **7** was prepared by $K_3Fe(CN)_6$ oxidation of **1** (4% yield) and was identified by spectral analysis of it and its derivatives (see Experimental Section). A series of known oxidative phenol coupling methods was applied to **1**, with the results summarized in Table I. As expected, relatively low yields of the intramolecularly coupled dienone **7** were obtained. The bulk of the unaccounted for material in each case was present as insoluble, intractable, presumably polymeric products; in no case was the isomeric ortho–para coupled dienone detected.

A bisperester derivative seemed to be a potentially suitable covalently bonded intermediate for diphenolic coupling. Consequently diphenol **1** was acylated with *tert*-butylperoxy chloroformate[8] in the presence of pyridine. The resulting crude bis(*tert*-butylperoxycarbonate) ester **8** was partially purified



8- R=$(CH_3)_3COOC-$
9- R=$VOCl_2$
7- R=H
10- R=OCH_3

by trituration with pentane and high vacuum evaporation of the volatile contaminants, but it was unstable to chromatographic conditions. The material so obtained was approximately 90% pure according to NMR integration, and contained 77% of the theoretical active oxygen according to iodometric titration.[9] Thermal decomposition of **8** in a variety of solvents (see Table II) proved very disappointing, however, affording only a 4% yield of dienone **7** in the best case. Since all solvents were anhydrous, hydrogen atom abstraction processes had to be responsible for the formation of diphenol **1**, at least in the aprotic cases.

Attention was then directed to inorganic oxidants that might satisfy the previously mentioned criteria. Funk and co-workers[10] reported that reaction of $VOCl_3$ with phenol or *p*-chlorophenol in refluxing hexane afforded crystalline substitution products of formula $VOCl(OAr)_2$ and $VO(OAr)_3$; they furthermore noted that more reactive phenols such as cresol and β-naphthol gave only complex oxidation products under these

Table III. Oxidative Coupling of Diphenols with $VOCl_3$

Substrate[a]	$VOCl_3$, mol equiv	Solvent	Temp, °C[b]	Dienone	Yield,[c] %
1	1.0	Et_2O	−78; 35	**7**	12
1	2.0	Et_2O	−78; 35	**7**	50
1	2.5	Et_2O	−78; 35	**7**	76
1[d]	2.5	Et_2O	−78; 35	**7**	74
1	2.5	DME	−50; 25	**7**	70
4	2.5	Et_2O	−78; 35	**10**	69
11	2.5	CH_3CN	−20[e]	**12**	25
11	3.5	CH_3CN	−20[e]	**12**	50
11	3.5	DME	−50; 25	**12**	33

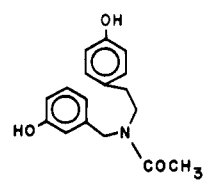
[a] Substrate was $1.1–2.5 \times 10^{-3}$ M in anhydrous, degassed solvent in each case. [b] Reaction mixture was maintained at the lower temperature for 1–3 h, and at the higher temperature for 3–12 h. [c] Yield of isolated, solid product. [d] Et_3N (2.0 mol equiv) was added just prior to warming. [e] For 50 h.

conditions.[11] *It therefore seemed feasible to generate the bis-*(dichlorovanadate) ester **9** by reaction of diphenol **1** with 2 mol equiv of $VOCl_3$ at low temperature, and then to effect the desired oxidative coupling of **9** at higher temperature. This approach proved remarkably successful (see Table III).

Addition of diphenol **1** to a dark red solution of $VOCl_3$ in anhydrous ether at −78 °C resulted in immediate evolution of HCl and a concomitant color change to deep blue; a portion of the reaction mixture quenched with water after 3 h at −78 °C was shown to contain only starting diphenol by TLC analysis. However, warming of the reaction mixture to reflux was accompanied by a color change to dark green, and it resulted in formation of dienone **7** in high yield (Table III). That the best yield of **7** (76%) was realized using 2.5 rather than 2.0 mol equiv of $VOCl_3$ was probably due to impurities in the commercial reagent and/or to incomplete removal of moisture from the system. There was some concern that residual HCl might be reducing the yield of **7** by catalyzing a dienone–phenol rearrangement; however, addition of triethylamine to the reaction mixture prior to warming had no measurable effect on the outcome. Similarly, utilization of 1,2-dimethoxyethane (DME) as reaction solvent had no significant effect.

In order to test the effect on the intramolecular coupling *reaction of having two phenolic moieties with considerably* different oxidation potentials, diphenol **4** was subjected to $VOCl_3$. The para–para coupled dienone **10** was obtained, again in good yield (Table III). Mass spectral analysis of the residual mixture indicated the presence of monochlorinated materials in this case, however, while no such analogous materials were detected when **1** was the substrate. In subsequent application of $VOCl_3$ to alkaloidal precursors, chlorination of *o*-methoxyphenol moieties was observed to be a competing side reaction to coupling in most cases.[12]

The effect on the $VOCl_3$ coupling reaction of increased chain length, as well as of the presence of a nitrogen function, was tested using the diphenolic acetamide **11.** Due to the insolubility of **11** in ether, acetonitrile and DME were utilized as solvents. The best yield (50%) of dienone **12** was realized with



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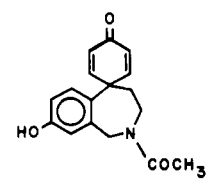

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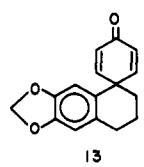
3.5 mol equiv of $VOCl_3$ in acetonitrile (Table III); the need for an additional equivalent of oxidant in this case was attributed to the amide moiety possibly reacting with, and deactivating, the $VOCl_3$. Nevertheless, a significant reduction in coupling yield relative to the simpler diphenolic substrates was observed with this substrate.

Subsequent to our initial report[4a] of the efficacy of $VOCl_3$ in intramolecular coupling, the reagent has been successfully employed for diphenolic coupling in syntheses of representatives of the Amaryllidaceae,[12,13] Erythrina,[14] hasubanan,[15] aporphine,[12,16] and homoaporphine[17] alkaloid classes.

Monophenolic and Nonphenolic Coupling. Intramolecular coupling of monophenolic substrates seemed a potentially attractive in vitro modification of the biosynthetic process, since high concentration of the oxidant would in principle not be necessary, and the intramolecularly coupled product would usually not be phenolic and thus would not be as susceptible to overoxidation. This approach would furthermore allow incorporation of *O*-alkyl substituents, such as the methylenedioxy moiety, which are usually biosynthetically introduced at a later stage in the pathway, at a conveniently early stage of the laboratory synthesis. However, the only example of such an intramolecular coupling that could be found at the time was a report of C–O coupling in the dichlorodicyanoquinone oxidation of 2-hydroxy-3′-methoxybenzophenones to the corresponding methoxyxanthones.[18]

Similar to our approach to diphenolic coupling, we initially sought a two-electron oxidant that could be covalently bonded to the phenol oxygen, and which could then be induced to undergo two-electron transfer either prior to or concerted with nucleophilic attack by the other aromatic ring. Although $VOCl_3$ was clearly capable of acting as a two-electron oxidant,[3h] our first attempts to effect coupling of monophenols **2** and **5** with this reagent resulted only in recovery of starting material (see Table IV, entries 8 and 13). However, an exactly analogous process had been proposed to account for the oxidative cleavage of 2,4,6-trisubstituted phenols to 2,6-disubstituted *p*-quinones by thallium(III) trifluoroacetate (TTFA).[19] We consequently applied the latter reagent to monophenolic coupling.[4b]

As indicated in Table IV, oxidative coupling of monophenol **5** with TTFA proceeded smoothly to afford the dienone **13** in high yield (entry 1). However, application of TTFA to the meta-substituted monophenol **2,** which upon para–para coupling could yield either dienone **7** by alkyl–oxygen cleavage[7b] or monophenol **14** by rearrangement and proton loss, sur-



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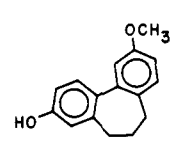

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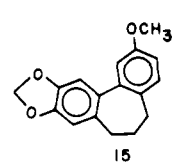

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Table IV. Oxidative Coupling of Monophenolic and Nonphenolic Substrates[a]

Entry No.	Substrate	Oxidant (mol equiv)	Temp, °C (time, h	Product (yield, %)[b]
1	**5**	TTFA (1.0)	25 (3)	**13** (88)
2	**2**	TTFA (1.0)	25 (12)	**2** (80)
3	**2**	TTFA (1.0)	25 (48)	**2** (98)
4	**2**	TTFA (1.5)	25 (12)	**2** (60)
5	**5**	AgO[c] (2.1)	−78 (1); −40 (1)	**5** (100)[d]
6	**5**[e]	$Ag(TFA)_2$[f] (2.0)	−60 (1); −30 (1)	**13** (83)
7	**5**	$VOCl_3$ (2.5)	−78 (6)	**13** (97)
8	**5**	$VOCl_3$ (2.5)	25 (5)	**13** (0); **5** (45)
9	**5**	$VOCl_3$ (2.5)[g]	−78 (5)	**13** (9); **5** (82)
10	**5**	$VOCl_3$ (2.5)[h]	−78 (6)	**13** (0); **5** (99)
11	**5**[i]	$VOCl_3$ (2.5)	−78 (10)	**13** (45); **5** (41)
12	**2**	$VOCl_3$ (2.5)	−78 (5)	**14** (99)
13	**2**[i]	$VOCl_3$ (2.5)	−78 (10)	**2** (100)[d]
14	**6**	$VOCl_3$ (2.5)	−78 (6)	**13** (70); **15** (18)
15	**6**	$VOCl_3$ (2.5)[h]	−78 (6)	**6** (98)

[a] Substrate was ca. 5×10^{-3} M in anhydrous, degassed solvent; the solvent was CH_2Cl_2 unless otherwise noted. [b] Yield of isolated material, homogeneous to TLC analysis, unless otherwise noted. [c] Reference 21. [d] By TLC analysis of the crude reaction mixture. [e] 2.3×10^{-2} M in CH_2Cl_2/CF_3COOH, 10:1. [f] Generated in situ from AgO and CF_3COOH. [g] Plus 3.0 mol equiv of Et_3N. [h] Plus 3.0 mol equiv of $(i\text{-}Pr)_2EtN$. [i] In Et_2O.

prisingly resulted in unchanged substrate as the only isolable material (entries 2–4) after passage of the reaction mixture through a silica gel column.

The potent oxidizing properties of silver(II) species[20] suggested their use in monophenolic coupling. Treatment of monophenol **5** with a suspension of silver(II) oxide[21] in dichloromethane gave no reaction (Table IV, entry 5), but addition of trifluoroacetic acid to the medium afforded a homogeneous mixture, presumably containing silver(II) trifluoroacetate, which rapidly oxidized **5** to dienone **13** in good yield (entry 6). It was interesting to note that 2 mol equiv of the oxidant was required and metallic silver was not a product of the reaction, thus rendering unlikely a concerted two-electron oxidation mechanism in this case.

The report by Kupchan and Liepa[22] of intramolecular coupling of monophenolic benzylisoquinolines using a variety of oxidants in acidic media, including VOF_3 in trifluoroacetic acid, led us to reexamine the utility of $VOCl_3$ in monophenolic coupling. In contrast to our earlier results (vide supra), we found that oxidation of monophenol **5** with $VOCl_3$ in dichloromethane afforded dienone **13** in virtually quantitative yield, *as long as the temperature was maintained at −78 °C throughout the reaction* (Table IV, entry 7). Under these conditions trifluoroacetic acid was unnecessary, and in fact there was no effect on the outcome when the same procedure was followed in the presence of 7.5 mol equiv of anhydrous trifluoroacetic acid. However, unlike diphenolic coupling with $VOCl_3$, increased reaction temperature (entry 8) or added triethylamine or ethyldiisopropylamine (entries 9 and 10) almost completely stopped the desired intramolecular coupling reaction. Similarly, substitution of ether for dichloromethane as reaction solvent significantly slowed the reaction (entry 11). Monophenol **2**, which had been essentially inert to TTFA, was coupled to the tricyclic phenol **14** in quantitative yield with $VOCl_3$ in dichloromethane (entry 12), but was unaffected by the same oxidant in ether (entry 13).

Oxidative coupling of a nonphenolic substrate[23] with $VOCl_3$ proved feasible at low temperature. Oxidation of **6** was accompanied primarily by alkyl–oxygen cleavage to give dienone **13** in 70% yield; however, a minor component whose spectral properties were consistent with **15**, the product of coupling followed by rearrangement, was also isolated in 18% yield. The presence of ethyldiisopropylamine again completely inhibited the oxidative coupling (Table IV, entries 14 and 15).

The results of the application of these monophenolic coupling methods to the synthesis of various alkaloids will be presented in the sequel.[4b,12]

Mechanistic Considerations. The fact that the oxidative coupling of diphenolic substrates with $VOCl_3$ was unaffected by added triethylamine or by changes in solvent basicity, while monophenolic and nonphenolic coupling with $VOCl_3$ was very sensitive to these factors, indicates that different mechanisms are operative in each case. It therefore seems likely that radical intermediates are involved in the diphenolic cases, despite the suggestion to the contrary;[3h] the unusually good yields of diphenolic coupling realized with $VOCl_3$ might then be due to some stabilization of the radical intermediates by complexation with vanadyl species, as has been observed with hydroxy and hydroperoxy radicals in the presence of oxyvanadium(V) ions.[24] The similarity in behavior of $VOCl_3$ toward both monophenolic and nonphenolic substrates suggests that in both cases two successive one-electron oxidations are involved, and that coupling occurs at the cation radical stage.[7a]

It has been recently suggested that the oxidation of phenols by thallium(III) proceeds by way of ring-thallated intermediates.[19b] However, we have observed a remarkable directing effect in favor of ortho coupling in the oxidation of reticuline derivatives with TTFA,[25] for which an O-thallated intermediate seems to provide the only explanation. Similarly, Ronlan and co-workers[7a] have ascribed the differences they observed between anodic and TTFA coupling of diarylalkanes to thallium(III) phenolate intermediates. In either case, the question of whether coupling occurs concomitant with a concerted two-electron transfer, or via successive one-electron oxidations, is also an open one.

Experimental Section

Melting points were determined with a Kofler microscope hot stage and are uncorrected. Infrared spectra were obtained using a Perkin-Elmer 137 spectrophotometer; ultraviolet spectra were obtained using a Perkin-Elmer 202 or Cary14 spectrophotometer. NMR spectra were recorded on Varian A-60, Bruker HX-90, or HX-270 spectrometers; chemical shifts are reported in parts per million downfield from tetramethylsilane (δ) and coupling constants in hertz. Mass spectra were obtained on an AEI MS 902 instrument. Elemental analyses were carried out by M-H-W Laboratories, Garden City, Michigan. Thin layer chromatographies were done on silica gel unless otherwise noted; developed plates were visualized under ultraviolet light and/or by

spraying with saturated ceric sulfate in 10% aqueous H_2SO_4 followed by heating on a hot plate.

Anhydrous solvents were prepared as follows: ether, commercial reagent-grade "anhydrous" ether was stored over freshly cut sodium ribbon for at least 24 h prior to use; dichloromethane and acetonitrile, the solvent was refluxed over and distilled from P_2O_5 and was stored in sealed containers over 3 Å molecular sieves; 1,2-dimethoxyethane, the solvent was distilled from lithium aluminum hydride immediately prior to use. Solvents were "degassed" by entrainment with prepurified nitrogen for 0.5 h prior to use.

Chalcones. General Procedure. To a solution of NaOH in 95% ethanol or NaOEt in absolute ethanol was added the benzaldehyde and the acetophenone, and the mixture was stirred at 25 °C for 20–24 h. Concentrated HCl was added to neutrality and most of the ethanol was removed under reduced pressure. The residue was partitioned between ethyl acetate and water; the organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to afford the crude chalcone.

3,4′-Dimethoxychalcone. From 2.70 g (20 mmol) of 3-methoxybenzaldehyde, 3.00 g (20 mmol) of 4-methoxyacetophenone, and excess NaOEt in 50 mL of ethanol there was obtained 5.1 g (95%) of the crude chalcone, mp 92–96 °C. Recrystallization from ethanol gave 3,4′-dimethoxychalcone, mp 94–96 °C (lit.[26] mp 96–97 °C): IR ($CHCl_3$) 6.01, 6.23, 6.33, 7.95, 8.54, 9.75, 12.02 μm; NMR ($CDCl_3$) 3.87 (s, 3), 3.89 (s, 3), 6.83–7.78 (m, 8), 8.09 (d, 2, J = 9 Hz).

3-Benzyloxy-4′-methoxychalcone. From 5.02 g (24 mmol) of 3-benzyloxybenzaldehyde, 3.60 g (24 mmol) of 4-methoxyacetophenone, and 2.0 g (50 mmol) of NaOH in 70 mL of 95% ethanol there was obtained 7.34 g of the crude chalcone. Recrystallization from ethanol–water afforded 6.63 g (80%) of 3-benzyloxy-4′-methoxychalcone, mp 137–138 °C: IR ($CHCl_3$) 6.05, 6.25, 7.55, 7.67, 8.01, 8.60, 9.81, 10.25, 12.05 μm; NMR ($CDCl_3$) 3.80 (s, 3), 5.03 (s, 2), 6.89 (d, 2, J = 9 Hz), 7.16–7.61 (m, 11), 7.96 (d, 2, J = 9 Hz).

4-Methoxy-3,4′-dibenzyloxychalcone. From 3.00 g (12.4 mmol) of 3-benzyloxy-4-methoxybenzaldehyde,[27] 2.70 g (11.9 mmol) of 4-benzyloxyacetophenone, and excess NaOEt in 100 mL of ethanol there was obtained, after recrystallization from ethanol, 2.8 g (52%) of the chalcone, mp 140–147 °C. Recrystallization from benzene–methanol–hexane gave 4-methoxy-3,4′-dibenzyloxychalcone, mp 152–155 °C: IR ($CHCl_3$) 6.01, 6.23, 6.62, 7.95, 8.55, 8.79, 9.77 μm; NMR ($CDCl_3$) 3.93 (s, 3), 5.17 (s, 2), 5.23 (s, 2), 6.95–7.68 (m, 17), 8.05 (d, 2, J = 9 Hz).

4′-Benzyloxy-3,4-methylenedioxychalcone. From 14.2 g (94.7 mmol) of 3,4-methylenedioxybenzaldehyde, 21.3 g (94.2 mmol) of 4-benzyloxyacetophenone, and 8.0 g (200 mmol) of NaOH in 300 mL of 95% ethanol there was obtained 32.6 g (97%) of 4′-benzyloxy-3,4-methylenedioxychalcone, mp 143–146 °C: IR ($CHCl_3$) 6.01, 6.23, 6.64, 6.70, 6.90, 8.01, 8.55, 9.60 μm; NMR ($CDCl_3$) 5.10 (s, 2), 5.97 (s, 2), 6.80–7.67 (m, 12), 8.01 (d, 2, J = 9 Hz).

4′-Methoxy-3,4-methylenedioxychalcone. From 37.5 g (0.250 mol) of 3,4-methylenedioxybenzaldehyde, 37.5 g (0.250 mol) of 4-methoxyacetophenone, and 20 g (0.5 mol) of NaOH in 750 mL of 95% ethanol, there was obtained 70.0 g (99%) of 4′-methoxy-3,4-methylenedioxychalcone, mp 134–135 °C: IR ($CHCl_3$) 6.01, 6.23, 6.66, 6.71, 6.92, 8.02, 8.56, 9.60, 9.76 μm; NMR ($CDCl_3$) 3.85 (s, 3), 5.98 (s, 2), 6.72–7.67 (m, 7), 8.03 (d, 2, J = 9 Hz).

Diarylpropanes. General Procedure. A solution of the chalcone in 95% ethanol was purged with nitrogen for 0.5 h, then the appropriate amount (10% of the weight of chalcone) of 10% Pd/C was added. Hydrogen was introduced via a gas dispersion tube with stirring at 25 °C and 1 atm for 20 h; 5 drops of concentrated HCl was then added and hydrogenation was continued for an additional 20 h. The catalyst was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. The residue was partitioned between ether and water; the ether layer was washed with aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated under reduced pressure to afford the crude diarylpropane.

1-(3-Methoxyphenyl)-3-(4-methoxyphenyl)propane (3) and 1-(3-Hydroxyphenyl)-3-(4-hydroxyphenyl)propane (1). From 8.8 g (33 mmol) of 3,4′-dimethoxychalcone in 250 mL of ethanol was obtained 6.3 g of crude product. Distillation under reduced pressure afforded 4.4 g (52%) of the dimethyl ether **3** as a colorless oil homogeneous to TLC (hexane–chloroform, 1:1): bp 150–158 °C (0.2 mm); IR ($CHCl_3$) 6.22, 6.66, 8.06, 9.65, 12.02 μm; NMR ($CDCl_3$) 1.90 (m, 2), 2.58 (br t, 4), 3.72 (s, 6), 6.55–7.40 (m, 8).

A mixture of 4.4 g (17 mmol) of the dimethyl ether **3** and 15 g of freshly prepared anhydrous pyridine hydrochloride was heated at 210–215 °C under nitrogen for 1.5 h.[28] The resulting viscous oil was partitioned between ether and water, and the ether layer was extracted thoroughly with aqueous NaOH. The basic extract was acidified with HCl and was reextracted with ether; the organic layer was washed with water, dried over Na_2SO_4, and evaporated. The resulting red oil was subjected to molecular distillation and crystallization from benzene to give 1.8 g (46%) of the diphenol **1**, mp 72–74 °C. An analytical sample of **1** was prepared by repeated recrystallization from benzene: mp 76–78 °C; IR ($CHCl_3$) 2.79, 3.00, 6.28, 6.63, 6.91, 7.99, 8.54, 8.68, 12.04 μm; NMR (acetone-d_6) 1.79 (m, 2), 2.44 (br t, 4), 6.47–7.27 (m, 8).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.95; H, 7.02. Found: C, 79.22; H, 6.93.

1-(3-Hydroxyphenyl)-3-(4-methoxyphenyl)propane (2). From 5.71 g (16.6 mmol) of 3-benzyloxy-4′-methoxychalcone in 900 mL of ethanol was obtained 3.43 g of crude product. Distillation under reduced pressure gave 2.72 g (68%) of monophenol **2** as a colorless, viscous oil: bp 150 °C (0.025 mm); IR ($CHCl_3$) 2.81, 3.03, 6.23, 6.32, 6.66, 6.92, 8.08, 8.53, 8.68, 9.68 μm; NMR ($CDCl_3$) 1.85 (m, 2), 2.50 (br t, 4), 3.68 (s, 3), 6.58–7.07 (m, 8).

Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.33; H, 7.43. Found: C, 79.14; H, 7.14.

1-(3-Hydroxy-4-methoxyphenyl)-3-(4-hydroxyphenyl)propane (4). From 20.3 g (45.1 mmol) of 4-methoxy-3,4′-dibenzyloxychalcone in 700 mL of ethanol was obtained 6.6 g of crude product. The oil was purified by molecular distillation at 120 °C under high vacuum, followed by crystallization from benzene, to give 3.70 g (32%) of diphenol **4** as a tan solid, mp 88–89 °C. An analytical sample was prepared by column chromatography on silica gel (elution with chloroform–2% ether) and crystallization from benzene, mp 89.5–91.5 °C: IR ($CHCl_3$) 2.83, 3.01, 6.20, 6.29, 6.89, 6.97, 7.90, 8.09, 8.55, 8.90, 9.70 μm; NMR ($CDCl_3$) 1.92 (m, 2), 2.57 (br t, 4), 3.85 (s, 3), 6.67–7.25 (m, 7).

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.51; H, 7.23.

1-(3,4-Methylenedioxyphenyl)-3-(4-hydroxyphenyl)propane (5). From 358 mg (1.00 mmol) of 4′-benzyloxy-3,4-methylenedioxychalcone in 200 mL of ethanol was obtained 225 mg (88%) of product which was homogeneous to TLC (chloroform–5% ethyl acetate), and which crystallized upon standing. Recrystallization from benzene–hexane afforded **5** as a white solid, mp 73.5–74 °C: IR ($CHCl_3$) 2.83, 3.04, 6.22, 6.65, 6.74, 6.98, 8.05, 8.46, 8.55, 9.63, 10.63, 12.03, 12.33 μm; NMR ($CDCl_3$) 1.87 (m, 2), 2.53 (br t, 4), 5.87 (s, 2), 6.66–7.10 (m, 7).

Anal. Calcd for $C_{16}H_{16}O_3$: C, 75.00; H, 6.25. Found: C, 74.92; H, 6.22.

1-(3,4-Methylenedioxyphenyl)-3-(4-methoxyphenyl)propane (6). From 1.72 g (6.10 mmol) of 4′-methoxy-3,4-methylenedioxychalcone in 600 mL of ethanol was obtained 1.50 g (91%) of **6** as a pale orange oil. An analytical sample was prepared by preparative TLC (hexane–2% ether) to give **6** as a colorless oil: IR ($CHCl_3$) 6.21, 6.65, 6.76, 6.98, 7.73, 8.05, 8.51, 9.62, 10.61, 12.30 μm; NMR ($CDCl_3$) 1.92 (m, 2), 2.57 (br t, 4), 3.77 (s, 3), 5.88 (s, 2), 6.63–7.17 (m, 7).

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.56; H, 6.67. Found: C, 75.53; H, 6.77.

Oxidation of 1 with Potassium Ferricyanide. Characterization of Dienone 7. A solution of 240 mg (1.05 mmol) of diphenol **1** in 300 mL of $CHCl_3$ was added to a solution of 450 mg (1.37 mmol) of $K_3Fe(CN)_6$ and 2.25 g of Na_2CO_3 in 75 mL of water, and the mixture was stirred at room temperature under nitrogen for 9 h. The layers were separated and the aqueous layer was neutralized with dilute HCl, and was extracted with ether and ethyl acetate. All of the organic layers were combined, washed with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give 115 mg of a dark brown gum. The component less polar than starting material was isolated by preparative TLC ($CHCl_3$–1% methanol, continuous elution) of the crude mixture to yield 8 mg (3.4%) of dienone **7**, mp 200–215 °C. Sublimation at 100 °C (10^{-3} mm) and recrystallization from ethyl acetate afforded **7** as a white solid, mp 221–222 °C: IR (KBr) 3.22, 6.07, 6.74, 7.82, 11.62, 11.73, 12.29 μm; UV (EtOH) 237 (ε 29 900), 280 nm (ε 2570); NMR (Me_2SO-d_6) 1.80 (m, 4), 2.10 (s, 1, OH), 2.80 (m, 2), 6.20 (d, 2, J = 10 Hz), 6.65 (m, 3), 7.16 (d, 2, J = 10 Hz).

Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.65; H, 6.19. Found: C, 79.78; H, 6.26.

A solution of 50 mg (0.22 mmol) of dienone **7** in 2 mL of pyridine and 1 mL of acetic anhydride was warmed on a steam bath overnight. The mixture was diluted with ether and was extracted with 10% aqueous HCl, 1 N aqueous NaOH, and water. The ether layer was dried over Na_2SO_4 and evaporated. The solid residue was recrystallized twice from acetone–hexane and twice from methanol, then sublimed at 100 °C (10^{-3} mm), to give the pure acetylated dienone **7-OAc**, mp 169–171 °C: IR ($CHCl_3$) 5.71, 6.02, 6.75, 8.73, 9.84 μm; NMR ($CDCl_3$) 1.84 (m, 4), 2.24 (s, 3), 2.89 (m, 2), 6.20 (d, 2, J = 10 Hz), 6.90 (m, 5).

Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.12; H, 5.97. Found: C, 76.14; H, 5.92.

To a solution of 50 mg (0.22 mmol) of dienone **7** in 50 mL of absolute ethanol was added 5 mg of 10% Pd/C and the mixture was hydrogenated at 1 atm and room temperature for 14 h. The catalyst was removed by filtration through Celite 545 and the filtrate was evaporated to give 35 mg (69%) of slightly impure tetrahydro derivative. Preparative TLC ($CHCl_3$, continuous elution) purification and recrystallization from ethyl acetate afforded the pure spiro ketone **7-H$_4$**, mp 163–166 °C: IR ($CHCl_3$) 2.77, 2.95, 5.84, 6.68, 7.36, 9.82 μm; NMR (Me_2SO-d_6) 1.70–2.80 (m, 15), 6.4–7.3 (m, 3). The signals in the 6.4–7.3 region were virtually identical with those shown by the 3,4-disubstituted phenol 17-α-ethynylestradiol.[29]

Gas Chromatographic Analysis of Mixtures of Diphenol 1 and Dienone 7. A mixture of known amounts of diphenol **1**, dienone **7**, and triphenylmethane was prepared, and was trimethylsilylated by addition of 1–3 mL of Tri-Sil (Pierce Chemical Co.) followed by warming on a steam bath for 2 min. The resulting cloudy solution was analyzed by injection on a 5 ft by ⅛ in. column packed with 3% SE-30 on 100–120 mesh DMCS treated Chromosorb W at 185 °C (flame ionization detector); the respective retention times were 15.3, 13.0, and 5.5 min. Peak areas were measured by triangulation and molar responses relative to triphenylmethane were calculated, with a relative average deviation over four analyses of less than 5%. The mixture was hydrolyzed by warming with 10% aqueous NaOH–ethanol (1:1) for 15 min, then was neutralized with 10% HCl and extracted with ether. The residue after evaporation of the ether was trimethylsilylated and analyzed as before, with no change in the relative peak areas. This technique was subsequently used for gas chromatographic (GC) analysis of crude reaction mixtures from oxidative coupling of **1**, after addition of a weighed quantity of triphenylmethane.

Oxidation of 1 with Ferric Chloride. To a solution of 40 mg (0.175 mmol) of diphenol **1** in 100 mL of degassed water–*tert*-butyl alcohol (2:1) was added 240 mg (0.89 mmol) of $FeCl_3 \cdot 6H_2O$, and the resulting solution was stirred in the dark at 50 °C for 20 h. Most of the alcohol was removed by evaporation under reduced pressure, and the residue was extracted with $CHCl_3$. The organic layer was washed with water, dried over Na_2SO_4, and evaporated. The resulting crude product was analyzed by GC as above (see Table I).

Oxidation of 1 with Silver Nitrate. To a solution of 50 mg (0.22 mmol) of diphenol **1** in 100 mL of anhydrous acetonitrile–ether (1:1) was added 10 mg (0.42 mmol) of NaH, and the mixture was stirred at room temperature under nitrogen for 20 min. The reaction mixture was cooled to −60 °C in a dry ice–acetone bath, 71 mg (0.42 mmol) of $AgNO_3$ was added, and stirring was continued at −60 °C for 30 min. The temperature was then raised to 80 °C and stirring was continued for 15 min, after which time the initial white suspension had turned black. The reaction mixture was acidified with HCl, the solids were removed by filtration, and the filtrate was extracted with ether. Preparative TLC ($CHCl_3$–3% methanol) of the residue after evaporation of the solvent afforded 8 mg (16%) of diphenol **1** as the only isolable material.

Oxidation of 1 with Silver Carbonate on Celite. A solution of 50 mg (0.22 mmol) of diphenol **1** in 5 mL of anhydrous ether was added to a suspension of 1.0 g of Ag_2CO_3–Celite[30] in 100 mL of anhydrous benzene, and the mixture was refluxed under nitrogen for 50 h. After removal of the solids by filtration and evaporation of the solvent, there was obtained 40 mg of a light yellow oil. Separation of the mixture by preparative TLC ($CHCl_3$–1% methanol, continuous elution) afforded 1 mg (2%) of dienone **7** and 36 mg (72%) of diphenol **1**.

Oxidation of 1 with Manganic Tris(acetylacetonate). To a solution of 40 mg (0.175 mmol) of diphenol **1** in 50 mL of degassed, anhydrous acetonitrile were added 310 mg (0.87 mmol) of $Mn(acac)_3$ (Baker Chemical Co.) and 3 μL of triethylamine, and the resulting dark solution was refluxed under nitrogen for 9 h.[31] The mixture was diluted with ether and washed with water. The residue after evaporation of the ether was subjected to GC analysis as before (see Table I).

Oxidation of 1 with Molybdenum Oxytetrachloride. A solution of 50 mg (0.22 mmol) of diphenol **1** in 75 mL of anhydrous ether was slowly added to a red solution of 140 mg (0.55 mmol) of $MoOCl_4$[32] (Climax Molybdenum Co.) in 100 mL of dry CCl_4 with stirring at −30 °C under nitrogen. The resulting blue-green solution was stirred at −30 °C for 3 h and at room temperature for 12 h. The light yellow reaction mixture was diluted with ether and washed with water. The organic layer was dried over Na_2SO_4 and evaporated; the residue was subjected to preparative TLC ($CHCl_3$–5% methanol) to yield 9 mg (18%) of dienone **7** and 13 mg (26%) of diphenol **1**.

Anodic Oxidation of 1. An H-type three-compartment electrolysis cell was fitted with a cylindrical platinum gauze anode and a mercury pool cathode, the respective compartments separated by a medium porosity glass frit. A reference electrode consisting of a silver wire immersed in 0.1 M $AgNO_3$ in acetonitrile was connected to the anode compartment by a salt bridge. The anode compartment was charged with a solution of 200 mg (0.877 mmol) of diphenol **1** in 150 ml of 0.2 M $NaClO_4$ in acetonitrile, and 10 mL of 5% aqueous NaOH was added. A constant potential of 0.2 V was applied with a potentiostat; the initial current of 20 mA dropped smoothly to 5 mA over a 3-h period. The reaction mixture was decanted and the brown solid residue that coated the compartment was triturated with water and $CHCl_3$. The combined solutions were neutralized with 10% HCl and the $CHCl_3$ layer was washed with water, dried over $NaSO_4$, and evaporated. The residue was subjected to preparative TLC ($CHCl_3$–5% methanol) to give 5 mg (2.5%) of dienone **7** and 10 mg (5%) of diphenol **1**.

Bis(*tert*-butylperoxycarbonate) Derivative 8. The procedure of Bartlett and Sakurai[8] was applied. A mixture of 1 mL of benzene and 6 mL of phosgene was cooled to 0 °C and 2 mL of freshly distilled *tert*-butyl hydroperoxide was added dropwise. The reaction mixture was stirred at 0 °C for 6 h, then was warmed to room temperature and the volatile components were removed in a stream of nitrogen. The residue was cooled to 0 °C and a solution of 900 mg (3.95 mmol) of diphenol **1** and 2 mL of pyridine in 8 mL of anhydrous ether was slowly added, and the mixture was left at 0 °C for 12 h. The solids were removed by filtration and the filtrate was evaporated under reduced pressure. Approximately half of the resulting oil was chromatographed on 15 g of Florisil in a jacketed column maintained at 0–5 °C, eluting with hexane–ether mixtures, but only diphenol **1** was recovered from the column.

The remaining crude product was dissolved in ether and was extracted with cold 10% aqueous NaOH, water, and saturated NaCl solution. The ether layer was evaporated and the residue was left under high vacuum for 12 h. The resulting oil was triturated with pentane and the pentane solution was concentrated under reduced pressure to afford 370 mg of the bis(*tert*-butylperoxycarbonate) derivative **8** as an oil: IR (CCl_4) 5.53, 7.34, 8.26, 8.50 μm; NMR (CCl_4) 1.37 (s, 16), 1.95 (m, 2), 2.64 (m, 4), 6.45–7.25 (m, 8). Iodometric titration of this material by the method of Silbert and Swern[9] gave a value of 77% of the theoretical active oxygen.

Thermal Decomposition of 8. An ampule containing a solution of 50 mg (0.11 mmol) of peroxy ester **8** in 50 mL of anhydrous solvent was entrained with nitrogen and then was degassed with two freeze–thaw cycles under vacuum. The ampule was sealed under vacuum and was immersed in an oil bath maintained at 125 °C for 4 h. The solvent was evaporated and the residue was subjected to GC analysis by the method previously detailed. For solvents used, and the results obtained, see Table II.

Oxidation of 1 with Vanadium Oxytrichloride. A 300-mL three-necked round-bottom flask equipped with a magnetic stirring bar, septum, reflux condenser, and pressure-equalizing dropping funnel was dried in an oven and cooled under nitrogen. Degassed anhydrous ether (100 mL) was added, the flask was immersed in a dry ice–acetone bath, and 120 μL (220 mg, 1.27 mmol) of $VOCl_3$ (Ventron Corp., Alfa Products; used without purification) was injected. The red solution was stirred at −78 °C under nitrogen while a solution of 114 mg (0.500 mmol) of diphenol **1** in 100 mL of degassed anhydrous ether was added via the dropping funnel over a period of ca. 5 min. The resulting deep blue solution was maintained at −78 °C for 2.5 h, then was brought to reflux over a period of 0.5 h, and was refluxed under nitrogen for 10 h. The dark green reaction mixture was quenched with water, and the ether layer was washed with water, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting off-white solid was recrystallized from ethyl acetate to afford 85 mg (76%) of dienone

7, mp 220–221 °C.

The same procedure was followed using anhydrous 1,2-dimethoxyethane as solvent, except that the reaction mixture was maintained at −50 °C for 3 h and at room temperature for 12 h.

Oxidation of 4 with Vanadium Oxytrichloride. The same procedure was followed using 43 mg (0.17 mmol) of diphenol **4** and 40 μL (73 mg, 0.42 mmol) of $VOCl_3$ in 100 mL of ether. The resulting crude product (42 mg) was separated by preparative TLC ($CHCl_3$, continuous elution) to give 30 mg (69%) of dienone **10**, mp 134–138 °C. Recrystallization from benzene–methanol afforded pure **10**, mp 140.5–141.5 °C: IR ($CHCl_3$) 2.84, 2.99, 6.01, 6.64, 7.87, 8.99, 11.65 μm; NMR ($CDCl_3$) 1.91 (m, 4), 2.81 (m, 2), 3.77 (s, 3), 6.29 (d, 2, J = 10 Hz), 6.38 (s, 1), 6.72 (s, 1), 7.06 (d, 2, J = 10 Hz).

Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.61; H, 6.25. Found: C, 74.47; H, 6.20.

***N*-Acetyl-*N*-(3-hydroxybenzyl)-4-hydroxyphenethylamine (11).** A mixture of 3.05 g (25.0 mmol) of 3-hydroxybenzaldehyde, 4.34 g (25.0 mmol) of 4-hydroxyphenethylamine hydrochloride, and 2.5 g of $NaHCO_3$ in 250 mL of absolute methanol was stirred at room temperature for 30 min and was warmed on a steam bath for 10 min. The mixture was cooled to 0 °C, 5.0 g of $NaBH_4$ was added slowly, and stirring was continued at room temperature for 1 h. Most of the methanol was removed under reduced pressure, 100 mL of water was added, and the mixture was brought to pH 7 by addition of HCl. The resulting precipitate was collected by filtration; the filtrate was extracted with ethyl acetate and the organic layer dried over Na_2SO_4 and evaporated. The solid residue was combined with the previously obtained precipitate to afford 5.45 g (90%) of the secondary amine as a tan solid. Recrystallization from absolute ethanol gave the amine as an off-white solid, mp 189–192 °C.

A solution of 500 mg (2.06 mmol) of the secondary amine in 1 mL of pyridine and 2 mL of acetic anhydride was warmed on a steam bath for 6 h. The mixture was diluted with ethyl acetate and extracted with dilute HCl and water, then dried over Na_2SO_4 and evaporated. The residue was dissolved in 30 mL of methanol–5% water, excess solid Na_2CO_3 was added, and the mixture was refluxed for 4 h. The solution was concentrated under reduced pressure, water was added, and the mixture was acidified with HCl and extracted with ethyl acetate. Evaporation of the organic layer afforded 528 mg (90%) of the acetamide **11** as a colorless oil, homogeneous to TLC ($CHCl_3$–3% methanol), which could not be induced to crystallize even after molecular distillation at 155 °C (0.02 mm): IR (KBr) 2.99, 6.17, 6.28, 6.62, 6.91, 7.35, 8.12, 10.06, 12.04 μm; NMR (acetone-d_6) 2.00 and 2.12 (3), 2.77 (t, 2, J = 7 Hz), 3.52 (m, 2), 4.52 and 4.67 (2), 6.7–7.4 (m, 8).

A 250-mg (0.877 mmol) sample of diphenolic acetamide **11** was reacetylated by heating with acetic anhydride in pyridine on a steam bath for 2 h. There was obtained 280 mg (87%) of solid product which upon recrystallization from ethyl acetate–hexane gave the pure *O,O*-diacetyl derivative of **11**, mp 96.5–97.5 °C: IR (KBr) 5.80, 6.13, 7.37, 8.28, 9.98, 11.00 μm.

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.24; H, 6.35; N, 3.53.

Oxidation of 11 with Vanadium Oxytrichloride. To a stirred solution of 112 μL (205 mg, 1.18 mmol) of $VOCl_3$ in 100 mL of degassed anhydrous acetonitrile maintained at −40 °C was added a solution of 95 mg (0.33 mmol) of the diphenol **11** in 100 mL of the same solvent, and the mixture was stirred at −20 °C for 50 h under nitrogen. The reaction mixture was partitioned between ethyl acetate and water; the organic layer was washed with water, dried over Na_2SO_4, and evaporated under reduced pressure to give 87 mg of a brown gum. Separation of the mixture by preparative TLC ($CHCl_3$–10% ethyl acetate–5% ethanol, continuous elution) afforded 47 mg (50%) of dienone **12** as a solid. Recrystallization from methanol–ethyl acetate gave the pure dienone, mp 267–270 °C: IR (KBr) 3.14, 6.02, 6.14, 6.22, 6.96, 7.68, 8.12, 8.51, 10.19, 11.67 μm; NMR (Me_2SO-d_6) 1.97 and 2.03 (3), 2.22 (t, 2, J = 6 Hz), 3.72 (t, 2, J = 6 Hz), 4.64 (s, 2), 6.13 and 6.14 (d, 2, J = 10 Hz), 6.47–6.83 (m, 3), 6.97 and 7.16 (d, 2, J = 10 Hz); UV (CH_3CN) 235 (ε 24 700), 280 nm (ε 2950); molecular ion at *m/e* 283.1202 (calcd for $C_{17}H_{17}NO_3$, 283.1208).

Oxidation of 5 with Thallium(III) Trifluoroacetate. To a slurry of 272 mg (0.501 mmol) of TTFA (Ventron Corp., Alfa Products; used without purification, but weighed and transferred in a drybox under nitrogen) in 100 mL of anhydrous CH_2Cl_2 was added 128 mg (0.500 mmol) of monophenol **5**, and the mixture was stirred under nitrogen at room temperature in the dark for 3 h. The resulting pale yellow solution was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and was passed through a column of silica gel, eluting with $CHCl_3$; evaporation of the eluate afforded 112 mg (88%) of dienone **13** as a yellow solid, homogeneous to TLC ($CHCl_3$). Recrystallization from methanol gave **13** as white crystals, mp 171 °C: IR ($CHCl_3$) 6.04, 6.17, 6.68, 6.78, 8.11, 9.63, 10.66, 11.41, 11.65 μm; NMR ($CDCl_3$) 1.97 (m, 4), 2.82 (m, 2), 5.85 (s, 2), 6.23 (d, 2, J = 10 Hz), 6.40 (s, 1), 6.60 (s, 1), 6.97 (d, 2, J = 10 Hz).

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.59; H, 5.51. Found: C, 75.26; H, 5.42.

Oxidation of 5 with Silver(II) Trifluoroacetate. A slurry of 124 mg (1.00 mmol) of AgO[21] in 15 mL of anhydrous CH_2Cl_2 was cooled to −60 °C, 2 mL of CF_3COOH was added, and the mixture was stirred at −60 °C for 15 min. To the resulting solution was added a solution of 128 mg (0.500 mmol) of monophenol **5** in 5 mL of anhydrous CH_2Cl_2, and the red mixture was stirred under nitrogen for 1 h at −60 °C and for 1 hr at −30 °C. The reaction mixture was quenched by addition of enough 10% aqueous Na_2CO_3 to render it alkaline; the resulting precipitate was filtered and washed with $CHCl_3$. The combined filtrates were separated and the organic layer was washed with water, dried over Na_2SO_4, and evaporated to give 106 mg (83%) of dienone **13** as a yellow solid homogeneous to TLC ($CHCl_3$).

Oxidation of 5 with Vanadium Oxytrichloride. The procedure described for the $VOCl_3$ oxidation of **1** was followed, using 120 μL (220 mg, 1.27 mmol) of $VOCl_3$, 128 mg (0.500 mmol) of monophenol **5**, and 200 mL of degassed anhydrous CH_2Cl_2. After addition of **5**, the resulting burgundy solution was stirred at −78 °C under nitrogen for 6 h, then immediately quenched by addition of 200 mL of cold water. The organic layer was washed with water, dried over Na_2SO_4, and evaporated to give 123 mg (97%) of crystalline dienone **13**, identical in all respects with the previously prepared compound.

Oxidation of 2 with Vanadium Oxytrichloride. The above procedure was followed using 121 mg (0.500 mmol) of monophenol **2**, affording 119 mg (99%) of tricyclic phenol **14** as a viscous colorless oil, homogeneous to TLC (benzene–25% ethyl acetate): IR ($CHCl_3$) 2.82, 2.99, 6.25, 6.76, 6.94, 7.91, 8.16, 8.51, 9.09, 9.66, 10.64, 11.43, 11.70, 12.12 μm; NMR ($CDCl_3$) 1.90–2.78 (m, 3), 3.85 (s, 3), 6.68–7.25 (m, 6); mass spectrum (70 eV) *m/e* 240, 181, 165, 152, 121, 91, 77; molecular ion at *m/e* 240.1177 (calcd for $C_{16}H_{16}O_2$, 240.1150).

Oxidation of 6 with Vanadium Oxytrichloride. The above procedure was followed using 135 mg (0.500 mmol) of nonphenolic substrate **6**, affording a mixture of two compounds (TLC) that was separated by preparative TLC (hexane–20% ether). The more polar fraction yielded 89 mg (0.35 mmol, 70%) of crystalline dienone **13**, identical with the previously prepared material. The less polar fraction gave 24 mg of an oil, the spectral properties of which were consistent with structure **15**: IR ($CHCl_3$) 6.23, 6.70, 6.78, 6.95, 7.05, 7.43, 7.86, 8.08, 8.57, 9.26, 9.63, 10.70, 11.61, 12.23 μm; NMR ($CDCl_3$) 1.96–2.26 (m, 2), 2.31–2.72 (m, 4), 3.83 (s, 3), 5.95 (s, 2), 6.71–7.15 (m, 5); mass spectrum (70 eV) *m/e* 268, 195, 165, 152, 135, 121.

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Factors Governing the Influence of a First Hydrogen Bond on the Formation of a Second One by the Same Molecule or Ion

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Abstract: The formation of a hydrogen bond l_1 between an acid AH and a base B weakens the electron-acceptor power of the other neighboring acidic sites of the acid and the strength of the other electron-donor sites of the base. As a consequence, the formation constants K_2 of the hydrogen bonds involving these additional sites and a ligand are smaller in the presence of bond l_1 than the value K_2^0 of the bond between the same site and the same ligand but in absence of l_1. The reverse is observed for secondary basic sites of the acid AH and acceptor sites of the base B for which the formation of l_1 enhances the addition constants K_2 with a ligand, compared with K_2^0 in the absence of bond l_1. The ratios K_2/K_2^0 are computed from the literature and are compared with the equilibrium constant K_1 of bond l_1, and the frequency shift $(-\Delta\nu_{AH})_1$ brought about by its formation. The data refer to the following cases: (1) the interaction of a second phenol molecule *with one of the lone pairs of electrons of a first one*, the latter being or being not involved in a OH···N bond with tetramethylurea or triethylamine; (2) the addition of a second phenol molecule *on the second basic site of a halogenide ion*, the first site of which can be involved in a X^-···HO hydrogen bond with the same phenol; (3) the interaction of pyridines or amines with the *second N–H site of a dialkyl- or monoalkylammonium ion*, the first N–H group of which can be involved in a N^+H···X^- or N^+H···L bond, respectively, with a counterion or with another ligand molecule. It is shown that although in a given family a correlation often exists between $\log K_2/K_2^0$ and $\log K_1$, the correlations between $\log K_2/K_2^0$ and $(-\Delta\nu_{AH})_1$ are much more general. This demonstrates that the leading factor governing the ratios K_2/K_2^0 for the additional sites is not the stability constant K_1 of the hydrogen bond l_1, but rather the perturbation of the AH distance brought about by the first bond and reflected by the frequency shift, and this irrespective of the charge of the partners. The influence of the first bond on the reactivity of the other specific sites has thus rather a covalent than an electrostatic character.

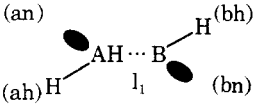
Many molecules or ions bear more than one specific site which can act as electron donor or electron acceptor in the formation of hydrogen bonds. This is the case, for instance, for the monoalkyl- and dialkylammonium ions which possess several electron-acceptor NH groups, the alcohols and phenols which are present near the acidic OH site, lone pairs of electrons which can act as electron donor sites, the halogenide ions which bear several electron donor sites, and so on.

The formation of a first hydrogen bond by a molecule or by an ion brings about displacements of the electron clouds and of the nuclei which affect the reactivity of the other specific sites of the partners. From a qualitative point of view it can be said, in agreement with the theories of Frank and Wen[1] and of Gutmann,[2] that a first hydrogen bond involving a given site of a molecule or ion weakens the reactivity of the neighboring sites of the same nature, whereas it enhances the electron-donor or -acceptor power of the adjacent sites of opposite nature.[3]

From a quantitative point of view, the donor or acceptor power of a given site can be described by the stability constant K_2 of the bond this site forms with a reference ligand.

This stability constant can be affected by the formation of a bond l_1 by the first site.

Let us consider, for instance, a first hydrogen bond between an acid AH and a base B, which in addition each still bear one acceptor and one donor site. We will call the secondary acceptor sites "ah" and "bh" and the donor sites "an" and "bn".



We now consider the equilibrium constant of the formation of a hydrogen bond with a ligand, respectively K_2 in the presence of bond l_1, and K_2^0 in absence of bond l_1.