s, 2867 m, 1845 m, 1590 s, 1560 s, 1350 s, 1290 s, 909 s, 890 m, 639 m, 629 m cm^{-1}; UV (MeOH) 430 nm (log ϵ 4.49), 320 (4.36); MS Calcd for $C_{41}H_{55}NO_2$, 593.42327; MS Obsd, 593.42387.

1,2-Bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(3,5-diisopropyl-4-imino-2,5-cyclohexadien-1-ylidene)cyclopropene (6b) and 1-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-(3,5-diisopropyl-4-aminophenyl)-3-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)cyclopropene (7b). These compounds were synthesized and purified by the method described for **6a** and **7a**.

6b: ^1H NMR (Me_2SO-d_6 and $CDCl_3$, 1:1) δ 1.04–1.24 (multiplet, 30 H), 1.48 (s, 18 H), 3.16 (septet, 2 H, broad), 6.96 (s, 2 H), 7.08–7.36 (multiplet, 5 H, broad), 7.62 (s, 2 H); IR (KBr) 3600 m, sh, 3400 w, broad, 3050 m, 2950 s, 2860 s, 1870 m, 1587 s, 1460 s, 1380 s, 1300 s, 1190 s, 1140 m, 972 m, 925 m, 890 m, 860 w, 877 m, 850 m cm^{-1}; UV (MeOH) 420 nm (log ϵ 4.54), 330 (4.07), 280 (4.26); MS Calcd for $C_{43}H_{59}NO_2$, 621.45457; MS Obsd, 621.45350.

Anal. Calcd for $C_{43}H_{59}NO_2$: C, 83.04; H, 9.56; N, 2.25; O, 5.15. Found: C, 82.80; H, 9.42; N, 2.20; O, 5.58.

7b: ^1H NMR ($CDCl_3$) δ 1.07 (d, 12 H), 1.25 (s, 18 H), 1.31 (s, 9 H), 1.47 (s, 9 H), 3.21 (septet, 2 H), 4.23 (s, 3 H, broad), 7.07 (s, 2 H), 7.09 (s, 2 H), 7.43 (d, 2 H, broad); IR ($CHCl_3$) 3610 m, sh, 3300 w, broad, 3200 w, broad, 2955 s, 2860 s, 1845 m, 1590 s, 1560 s, 1460 s, 1365 s, 1325 m, 1150 s, 1130 s, 908 s, 890 m, 638 m, 630 m cm^{-1}; MS Calcd for $C_{43}H_{59}NO_2$, 621.45457; MS Obsd, 621.45364.

Anal. Calcd for $C_{43}H_{59}NO_2$: C, 83.04; H, 9.56; N, 2.25; O, 5.15. Found: C, 83.06; H, 9.48; N, 2.14; O, 5.32.

1-(3,5-Diethyl-4-imino-2,5-cyclohexadien-1-ylidene)-2,3-bis(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)cyclopropane (1a). In a typical preparation, 0.200 g (0.3 mmol) of the combined mixture of **6a** and **7a** was slurried in 30 mL of benzene in an Erlenmeyer flask under a nitrogen atmosphere. To this slurry was added 0.200 g of lead dioxide, and the reaction mixture was stirred for 30 min. The lead dioxide was then filtered from the brilliant purple solution and the solvent was removed, leaving a metallic golden solid. The product was chromatographed on silica gel (hexane–ethyl ether, 9:1), giving **1a** in quantitative yield: ^1H NMR (CCl_4) δ 0.92–1.16 (multiplet, 15 H), 1.34 (s, 9 H), 1.40 (s, 9 H), 1.42 (s, 9 H), 2.40 (q, 4 H, broad), 6.18 (d, 1 H, broad), 6.92 (s, 3 H), 7.19 (d, 1 H, broad), 7.24 (d, 1 H, broad), 7.44 (d, 1 H, broad); IR ($CHCl_3$) 2963 s, 2880 w, 1750 m, 1610 s, 1600 s, 1485 m, 1410 m, 1365 m, 1255 m, 1093 s, 905 w, 881 w cm^{-1}; UV (cyclohexane) 539 (log ϵ 5.84), 500 sh (4.25), 280 (4.17); MS Calcd for $C_{41}H_{53}NO_2$, 591.40762; MS Obsd, 591.40682.

1-(3,5-Diisopropyl-4-imino-2,5-cyclohexadien-1-ylidene)-2,3-bis(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)cyclopropane (1b). **1b** was synthesized and purified by the method described for **1a**: ^1H NMR (CCl_4) δ 0.92 (s, 9 H), 1.08 (d, 6 H), 1.16 (d, 6 H), 1.33 (s, 9 H), 1.38 (s, 9 H), 1.40 (s, 9 H), 2.96 (septet, 2 H, broad), 6.26 (d, 1 H, broad) 7.14 (s, 3 H), 7.30 (d, 1 H, broad), 7.40 (d, 1 H, broad), 7.60 (d, 1 H, broad); IR ($CHCl_3$) 2965 s, 2878 w, 1750 m, 1610 sh, 1593 s, 1484 m, 1409 m, 1364 m, 1254 m, 1093 s, 905 w, 881 w, 810 w cm^{-1}; UV (cyclohexane) 539 nm (log ϵ 4.85), 500 sh (4.57), 280 (4.17).

Anal. Calcd for $C_{43}H_{57}NO_2$: C, 83.04; H, 9.24; N, 2.25; O, 5.47. Found: C, 83.09; H, 9.33; N, 2.14; O, 5.44.

Cyclic Voltammetry. A PAR Model 170 electrochemistry system was used with a three-electrode cell having platinum wire working and auxiliary electrodes and a saturated calomel reference electrode. All sample solutions were 1 mM in quinoid compound with 0.1 M tetrabutylammonium perchlorate as a supporting electrolyte in dichloromethane.

Electron Spin Resonance. About 2 mg of the quinoid compound and a small amount of tetrabutylammonium perchlorate were placed in an electrolytic ESR cell. A small piece of glass wool was placed between the electrodes to slow diffusion, and approximately 0.25 mL of dichloromethane was added as solvent. The cell was thoroughly degassed, and a minimal current necessary for a satisfactory signal was passed through the cell. Identical g values of 2.0027 were obtained for the anion radicals of **1a** and **1b**. The ESR spectra of the anion radicals of **1a** and **1b** are shown in Figures 1 and 2 and are described in the text.

Acknowledgment. We wish to thank Mr. John Jorgensen for stimulating discussions throughout the course of this work. This work was supported by Grants CHE74-01345A02 and CHE76-80374 from the National Science Foundation and by a grant from the 3M Company.

Registry No.—**1a**, 65276-72-4; **1b**, 65338-73-0; **6a**, 65276-73-5; **6b**, 65276-74-6; **7a**, 65276-75-7; **7b**, 65276-76-8; tetrachlorocyclopropene, 6262-42-6; 2,6-di-*tert*-butylphenol, 128-39-2; 2,6-diethylaniline, 579-66-8.

References and Notes

(1) R. West and D. C. Zecher, *J. Am. Chem. Soc.*, **92**, 155 (1970).
(2) R. West and D. C. Zecher, *J. Am. Chem. Soc.*, **92**, 161 (1970).
(3) S. K. Koster and R. West, *J. Org. Chem.*, **40**, 2300 (1975).
(4) R. West, D. C. Zecher, S. K. Koster, and D. Eggerding, *J. Org. Chem.*, **40**, 2295 (1975).
(5) L. A. Wendling, S. K. Koster, J. E. Murray, and R. West, *J. Org. Chem.*, **42**, 1126 (1977).
(6) K. Komatsu and R. West, *J. Am. Chem. Soc.*, in press.
(7) K. T. Finley and L. K. J. Tong in "The Chemistry of the Carbon–Nitrogen Double Bond", S. Patai, Ed., Wiley-Interscience, New York, N.Y., 1970, p 663.
(8) R. West, D. C. Zecher, and W. Goyert, *J. Am. Chem. Soc.*, **92**, 149 (1970).
(9) S. H. Glarum, *Rev. Sci. Instrum.*, **36**, 771 (1965).
(10) A. D. McLachlan, *Mol. Phys.*, **3**, 233 (1960).
(11) K. Komatsu and R. West, *J. Chem. Soc., Chem. Commun.*, 570 (1976).

Synthesis of Morphinandienones, a Dihydrophenanthrone, and Pummerer's Ketones by Anodic Coupling[1]

Larry L. Miller* and Ray F. Stewart

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

John P. Gillespie, Venkataraman Ramachandran, Ying Hung So, and Frank R. Stermitz

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received September 22, 1977

Anodic oxidations of several 1-benzyltetrahydroisoquinolines, laudanosine derivatives, were performed at platinum in acetonitrile containing sodium bicarbonate. Morphinandienones, flavinantine derivatives, were obtained in high yield. Oxidation of 4,4′-dimethoxy-2-methylbibenzyl anodically or with VOF_3 produced a dihydrophenanthrone. The anodic oxidation of several 4-alkylphenols to the corresponding Pummerer's ketones has been investigated, and improved yields are reported using aqueous acetonitrile as solvent and a carbon anode.

We have been interested for some time in the synthetic utility of anodic reactions which couple together activated aromatic rings. In this paper we explore three aspects of such anodic couplings. The first is an intramolecular coupling which produces morphinandienones. An improved procedure which gives very high yields is reported, and several approaches to compounds with the morphine substitution pattern are discussed. Second, the intramolecular coupling of 4,4′-dime-

0022-3263/78/1943-1580$01.00/0

thoxy-2-methylbibenzyl is described. This cyclization produces a dihydrophenanthrone with an angular methyl group, a structure equivalent to the steroidal A, B, C ring system. Finally, the intermolecular coupling of simple phenols to provide complex dimers known as Pummerer's ketones is described. This is a well-known oxidative process which normally proceeds in low yield. A more satisfactory electrochemical procedure is detailed.

Results and Discussion

Morphinandienone Syntheses. In previous papers[2,3] we have shown that anodic oxidation of 1-benzyltetrahydroisoquinolines (**1**) produces morphinandienones (**2**). This biomimetic reaction revealed the unrecognized synthetic possibilities available from nonphenolic oxidative coupling. This work has been followed by studies from several groups, using both chemical[4] and electrochemical[5] oxidations of suitable phenol ethers to procure alkaloid products. Our previous work produced morphinandienones in 30–50% yield by oxidation at platinum or carbon anodes in acetonitrile containing an electrolyte like lithium perchlorate or tetraethylammonium fluoroborate. The potential was controlled at ca. 1.1 V vs. Ag/Ag^{I},[6] and sodium carbonate was included to buffer the acid formed during oxidation. More detailed studies of this reaction have been undertaken.[7,8] Cyclic voltammetry revealed two waves for compounds **1**. The first at ca. 0.5 V was assigned to oxidation of the amine function, and the second at ca. 1.1 V was assigned to oxidation of a dimethoxy aromatic moiety. Most interestingly preparative oxidation of **1a** (see Table I) at the first wave led to aromatic coupling, and **2a** was isolated as usual. The mechanistic significance of this observation has been noted,[8] and it led to experiments in which weak acids, e.g., $NaHCO_3$, were added to the anolyte. We have shown using cyclic voltammetry that in the presence of 1% water $NaHCO_3$ protonates the amine functionality, protecting it from oxidation.

In the present study several 1-benzyltetrahydroisoquinolines were synthesized and preparative oxidations were performed in the presence of $NaHCO_3$. The synthesis generally followed the classical Bischler–Napieralski route. The compounds **1a–f, 3,** and **4** were isolated and identified spectrally. The new compounds **1c–f** gave satisfactory elemental analyses as well. Preparative oxidations were performed using a divided cell, a platinum anode, and a solvent mixture of 0.5% water in acetonitrile containing sodium bicarbonate and lithium perchlorate. Preparative oxidation of 1–5 mmol of **1a** at 1.1 V gave a 93% yield of **2a.** In comparison, the sodium carbonate procedure gave 55%. In Table I there are several other examples, all of which proceeded in satisfactory yield. Note, in particular, the oxidation of norlaudanosine (**1b**), which provides a general route to N-substituted derivatives. It seems clear that the utility of $NaHCO_3$ comes from some crude buffering capacity which prevents both amine oxidation and also acid-catalyzed rearrangements.[9] The product **2** is known to be quite sensitive to acid[10] and could be destroyed since two protons are produced at the anode per product molecule. A divided cell is used so that the anolyte acidity can become very high.

Table I. Substituents for 1 and 2 and Yield of 2[a]

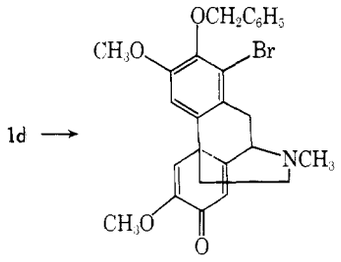
Registry no.	1	R	X	Yield of 2, %
1699-51-0	**1a**	CH_3	H	93
26642-09-1	**b**	H	H	91
65293-02-9	**c**	$CH_2CH{=}CH_2$	H	84
65293-03-0	**d**	*b*	*b*	94
65293-04-1	**e**	CH_3	Br	89
65293-05-2	**f**	CH_3	I	29

[a] Yield of **2** isolated from anodic oxidation of **1** in $NaHCO_3/H_2O/CH_3CN$ system; based on added starting material. Current yields were similar. [b] **1d** is 1-(2-bromo-3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline. It was oxidized to the corresponding bromomorphinandienone.

All oxidations of this type lead to the flavinantine substitution pattern of **2** via coupling at the 2′ position. Perturbing the coupling route to provide compounds with the morphine substitution pattern, e.g., **3,** via coupling at 6′[11] is obviously desirable. We have approached this problem by varying substituents on the benzyl ring. Because halogen substituents are easily attached and can be removed at some later stage, several halogenated analogues were synthesized and oxidized. Initial attempts involved 6′-halogen-substituted compounds which might block the usual coupling route. The use of 6′-bromolaudanosine was previously shown[3] not to produce the desired bromomorphinandienone, and this has now been affirmed for oxidation in the presence of sodium bicarbonate. Instead, cleavage of the bromo substituent, yielding **2a,** is the major route. In addition, an unsymmetrical dimer (NMR and mass spectra) was isolated but not fully characterized. The 6′-chloro compounds **4** and **7** were also prepared and oxidized. In each

case only cleavage products, e.g., **5**, **6**, and the aldehyde, were found after oxidation in either the sodium carbonate or bicarbonate media. Oxidations of **4** were also made at platinum in methylene chloride/trifluoroacetic acid. After workup the mixture appeared to contain no morphinandienone. It was reduced with sodium borohydride, and **6** was identified as a major component. Apparently the electron-withdrawing chlorine atom sufficiently deactivates the ring so that coupling at 2′ does not occur, and cleavage of the benzyl moiety takes over. This alternative pathway has many analogies in anodic chemistry[12] and mass spectroscopy. In particular, the mass spectra of the compounds **1a,d–f** show *m/e* 206, with the dimethoxytetrahydroisoquinolinium ion as the base peak.

The three halo analogues **1d–f** have been prepared and oxidized. The 2′-bromo compound **1d** cyclized without cleavage of bromine, indicating that the debromination previously found for 6′-bromolaudanosine came after the C–C bond formation of coupling.



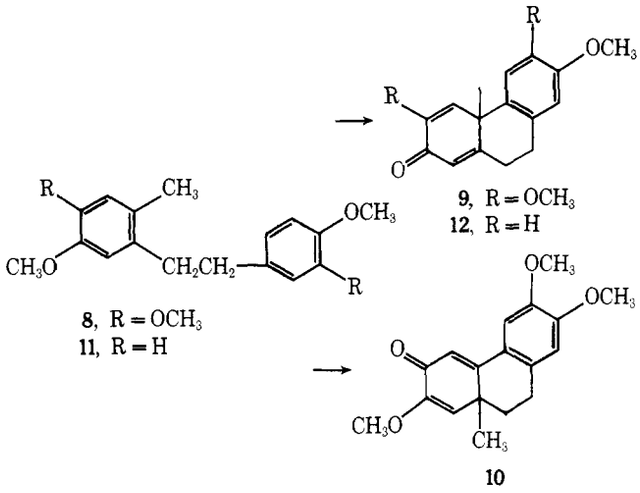
2d

The 5′ analogues were examined because it was hoped that the halo substituents would not be cleaved and would sterically impede coupling at the 6′ position. Morphinandienones were obtained in good yield from both the 5′-bromo and 5′-iodo compounds. The NMR spectra of these dienones suggested the structures **2e** and **2f** instead of the isomers **3**. In particular, the chemical shift of the vinyl proton in the 5 position of the dienone (δ 8.2) was taken into consideration. The structure **3** has a methoxy group in the 4 position which should deshield the proton at the 5 position to a value of δ 7.3.[13] Structure **2f** is, however, consistent with the spectrum since the presence of bulky iodine in the 4 position would have a larger deshielding effect on the C-5 proton. This assignment was confirmed by chemical reactions. Thus, the same reduction product, namely, *O*-methylflavinantinol, was obtained from the dienones **2e** and **2a** upon lithium aluminum hydride reduction.

The distinct preference for flavinantine-type coupling at the 6′ position rather than 2′ coupling can be explained by a combination of electronic and steric arguments. Coupling at the 6′ position is activated by a *p*-methoxy group and coupling at the 2′ position by an *o*-methoxy group. Coupling at 2′ is, however, disfavored by the *o*-methoxy inductive effect. Furthermore, coupling at 2′ should be sterically inhibited by the neighboring 3′-methoxy group. This might be especially severe since the methyl of the 3-methoxy needs to be in the plane of the ring to provide stabilization of incipient charge, and the most favorable conformation places the methyl of 3′-methoxy in front of the 2′ position. It is, nevertheless, surprising that the 5′-iodo compound still preferred cyclization at 6′ rather than 2′. As the NMR spectrum demonstrates, the steric requirements of iodine in **2f** are substantial.

It will be noted that the electrochemical route to morphinandienones of the type **2** is the only useful synthetic method to date. These compounds in turn serve as a useful starting point for the preparation of aporphines and dibenzazonines.[10]

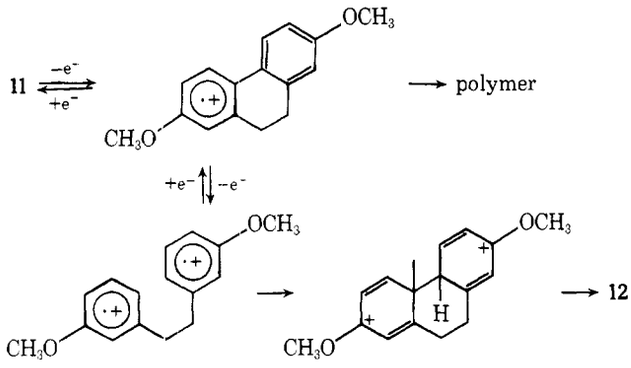
Dihydrophenanthrone Synthesis. In a previous study the electrooxidation of **8** was performed with the intent of preparing **9**.[14] In fact, a 90% yield of the rearranged product **10** was obtained. Kupchan and co-workers reported the same reaction occurred during oxidation of **7** with vanadium oxyfluoride in trifluoroacetic acid.[15] Consideration of the proposed mechanism for rearrangement suggested that the oxidation of **11** would produce an unrearranged product. This product is of interest because of its close relationship to several medicinal compounds[16] and because it represents a route to the A, B, C steroid rings[17] with the angular methyl group intact. Synthesis of **11** was achieved as detailed in the Experimental Section. Anodic oxidations at platinum in acetonitrile and in trifluoroacetic acid media were performed under several conditions. The cyclic voltammetric peak potential for 1 mM **11** in CH_3CN is 1.18 V. However, the most successful preparative oxidations were carried out at 1.8 V in acetonitrile with 2% water and solid sodium carbonate at 0 °C; Et_4NBF_4 was used as the electrolyte. After electrolysis, workup by evaporation, extraction with chloroform/water, and preparative thin-layer chromatography gave the product. Further purification by passage through a Sephadex column gave a pale yellow solid. The assignment of structure **12** is based on the compound's spectroscopic characteristics and by analogy to the coupling reactions reported in the literature. The $C_{16}H_{16}O_2$ molecular formula was indicated by mass spectroscopy and combustion analysis. The IR spectrum indicated the presence of a cross-conjugated cyclohexadienone system, and the NMR spectrum was consistent with structure **12**. Ultraviolet spectroscopy showed maxima at 233 and 272 nm. No absorption bands occurred beyond 300 nm, and this rules out the possibility of a conjugated, rearranged cyclohexadienone. The isolated yield of **12** was 22%, and 28% starting material was recovered when a charge of 3 F/mol was passed. In the absence of water or sodium carbonate, the current yield of dienone decreased to about 10% with 3 F/mol of electricity passed.



When the oxidation was performed at 1.20 V, the peak potential of the first wave, the current passing was only about 5 mA even with pulsing the anode potential to 0.0 V for 0.5 s every 30 s. The electrode was heavily coated with brown material. The same electrode coating problem occurred when nitromethane or a 1:2 mixture of trifluoroacetic acid and dichloromethane was used as solvent at 1.20 V.

Only 3% of **12** was obtained when **11** was oxidized at 1.2 V at a platinum electrode in acetonitrile with 0.1 M fluoroboric acid[5] as the supporting electrolyte after the passage of 2.2 F/mol. The electrode was also heavily coated with brown material. At 1.8 V, 18% of **12** was obtained after the passage of 3 F/mol and the electrode coating was less serious. In all cases, 1.8 V was the lowest potential at which a reasonable current could be passed.

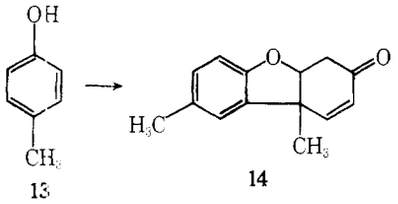
The need for high potentials can be understood if intermolecular coupling via cation radicals predominates at 1.2 V and intramolecular cyclization of a dication takes over at 1.8



V. These results and the explanation have analogy in the work of Parker and Ronlan on anodic oxidation of 3,4-dimethoxy-4′-methoxybibenzyl.[18] It should be noted that because of the high potential required for cyclization, the product **12** will not be totally stable and therefore the yields cannot be high.

Vanadium oxytrifluoride was also used. When **11** was stirred in trifluoroacetic acid with VOF_3 at either room temperature or at 0 °C for 45 min, only tar and trace amounts of starting material were obtained. At − 15 °C, 30% of dienone **12** and 22% of **11** were isolated after stirring for 2.5 h. It seemed to be useful to go to even lower temperatures, and in order to bring the temperature down to −30 °C[15] a 1:9 mixture of fluorosulfonic acid (FSO_3H) and CF_3COOH was used. **11** does not seem to survive in this solvent since neither it nor any dienone was detected after it was stirred in the solvent for 25 min without VOF_3.

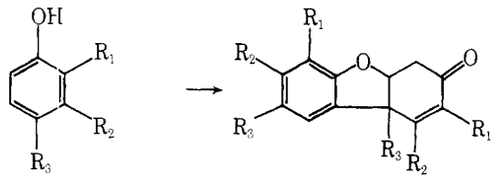
Ortho–Para Coupling of 4-Alkylphenols. Phenol oxidation reactions have held the interest of organic chemists for over a century. In addition to the intrinsic interest which was fed by the ease of oxidation of phenolate ions, phenol oxidations are thought to be important in the biosynthesis[19] of numerous natural products. In particular, the oxidative coupling of *p*-cresol (**13**) to Pummerer's ketone **14** has been often



13 14

cited as an analogue to usnic acid and morphine biosyntheses.[19]

Curiously there are to our knowledge no examples of high-yield conversions of **13** to **14**. Reported electrochemical routes give no more than a 10% yield of the ortho–para-coupled product. Recent advances in anodic coupling reactions have led us to further explore this route for several simple phenols;



13, $R_1 = R_2 = H$; $R_3 = CH_3$ **14**, $R_1 = R_2 = H$; $R_3 = CH_3$
15a, $R_1 = H$; $R_2 = R_3 = CH_3$ **16**, $R_1 = H$; $R_2 = R_3 = CH_3$
b, $R_1 = R_3 = CH_3$; $R_2 = H$ **17**, $R_1 = R_3 = CH_3$; $R_2 = H$
c, $R_1 = R_2 = H$; $R_3 = Et$ **18**, $R_1 = R_2 = H$; $R_3 = Et$

the results are given in Table II. The conditions used here, a carbon anode in 5% aqueous acetonitrile containing 1 equiv of base, are analogous to those used by Bobbitt for phenolic alkaloid oxidations.[20] We note that the yields based on reacted phenols are consistently higher than other methods, and in most cases pure crystalline compounds are readily obtained by simple column chromatography. The procedure described is the best of several evaluated. In particular, a carbon anode is important. Platinum is useless as an anode because it is rapidly passivated by a polymeric film. Reactions in which the phenoxide was produced using tetraethylammonium hydroxide in dry acetonitrile were unsuccessful as were reactions in aqueous sodium hydroxide.

Table II. Yield of Ketone Products

Registry no.	Reactant	Charge, F/mol	Product	Yield, %	Recovered reactant, %
106-44-5	**13**	1.0	**14**	37	50
95-65-8	**15a**	1.0	**16**	31	50
105-67-9	**b**	1.0	**17**	20	27
123-07-9	**c**	0.3	**18**	25	

The oxidation of 4-alkylphenols has been studied using a variety of chemical and electrochemical oxidizing systems.[21-23] The nature of the oxidant, the solvent, and pH are all important in determining the types of products formed. Strong chemical oxidants, nucleophilic solvents, and low pH favor nucleophilic trapping routes. In this manner it is possible to obtain good yields of synthetically useful 4-methyl-4-hydroxycyclohexadienones or 4-methyl-4-methoxycyclohexadienones.[24,25] Various mixtures of other products apparently derived from phenoxonium ions have also been described. Oxidations of *p*-cresol using a lead dioxide anode have been reported by Parker and Ronlan and produce high yields of hydroxycyclohexadienones.[24] Again cationic intermediates seem likely.

Reaction of phenols in basic media with mild oxidizing agents ($E_{1/2} < 1.0$ V) produces more dimeric products, and such conditions are employed here. The further problem in producing good yields of Pummerer's ketones is positional selectivity. In the present case it seems likely that surface chemistry on the anode is important. Bobbitt has reached a similar conclusion in his study of phenolic alkaloid oxidations performed under comparable conditions.[20]

Experimental Section

1-Benzyltetrahydroisoquinolines. Compounds **1a, 1b,** and **4** have been previously reported.[2,3] Data confirming the structural assignments are provided for compounds **1c–f** and **7.** Spectra of the intermediates are not reported, but were consistent with the proposed structures. An exemplary procedure is given below for the synthesis of 5′-bromolaudanosine.

***N*-(3,4-Dimethoxyphenethyl)-3-bromo-4,5-dimethoxyphenylacetamide.** To 24.1 g of 3-bromo-4-hydroxy-5-methoxybenzaldehyde in 75 mL of dimethylformamide (DMF) was added 20 mL of CH_3I and 25 g of anhydrous K_2CO_3. The mixture was heated at reflux for 3 h, poured into water, and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over Na_2SO_4 and evaporated in vacuo to yield 25.5 g (98%) of crude 3-bromo-4,5-dimethoxybenzaldehyde.

To 24.5 g of this benzaldehyde in 150 mL of ethanol was added excess $NaBH_4$ in small portions. After the addition was complete, the ethanol was removed in vacuo and a mixture of 5% aqueous NH_4Cl and $CHCl_3$ was added. The $CHCl_3$ layer was separated, dried, and evaporated to yield 24.1 g (97.5%) of crude 3-bromoveratryl alcohol.

A solution of 40 g of crude bromoveratryl alcohol in 500 mL of ether was treated with 9.8 mL of pyridine, and 49 g of $SOCl_2$ was added dropwise. The mixture was stirred for 3 h and then poured into 1 L of water. The aqueous solution was extracted with ether, and the ether was dried and evaporated to yield 50.6 g (96%) of crude 3-bromoveratryl chloride.

The crude chloride (49.6 g) in 250 mL of Me_2SO was heated for 1 h with 27.5 g (3 equiv) of NaCN. The solution was poured into water and extracted with $CHCl_3$. The $CHCl_3$ solution was washed five times

with H_2O, dried, and evaporated in vacuo to yield 43.9 g (91%) of crude 3-bromoveratronitrile.

The crude veratronitrile (43.3 g) was heated to reflux in 400 mL of 2 N NaOH for 12 h. The cooled solution was extracted with $CHCl_3$, acidified to pH 1, and reextracted with $CHCl_3$. This $CHCl_3$ solution was dried and evaporated in vacuo to yield 38.1 g (88%) of crude 3-bromo-4,5-dimethoxyphenylacetic acid.

A mixture of 25 g of this crude acid and 7.29 g (1.05 equiv) of 3,4-dimethoxyphenethylamine was heated at 160–180 °C for 3 h under a flow of argon. The black residue was dissolved in $CHCl_3$, extracted with 1 N NaOH and 1 N HCl, dried, and evaporated. The residue was dissolved in 70:30 EtOAc/cyclohexane, and the solution was passed through a silica gel plug. Evaporation of the solution yielded 32.4 g (81.3%) of *N*-(3,4-dimethoxyphenethyl)-3-bromo-4,5-dimethoxyphenylacetamide, mp 120–121 °C.

Anal. Calcd for $C_{20}H_{24}NO_5Br$: C, 54.93; H, 5.30; N, 3.20. Found: C, 54.89; H, 5.61; N, 3.18.

1-(3-Bromo-4,5-dimethoxybenzyl)-3,4-dihydro-2-methyl-6,7-dimethoxyisoquinolinium Iodide. The amide (20 g) was dissolved in 200 mL of CH_3CN, and 27 g of $POCl_3$ (6.5 equiv) was added dropwise over a 20-min period. The mixture was heated at reflux for 1 h, and the solution was evaporated in vacuo. The residue was dissolved in $CHCl_3$, and this solution was washed with water and 5% $NaHCO_3$. The $CHCl_3$ solution was dried and evaporated to give 19.7 g (96%) of crude product. This (18.2 g) was dissolved in 100 mL of EtOH and 25 mL of CH_3I, and the solution was heated at reflux for 12 h. The yellow 1-(3-bromo-4,5-dimethoxybenzyl)-3,4-dihydro-2-methyl-6,7-dimethoxyisoquinolinium iodide precipitated and was collected by filtration, mp 166–167 °C.

Anal. Calcd for $C_{21}H_{25}BrINO_4 \cdot H_2O$: C, 43.46; H, 4.69; N, 2.41. Found: C, 42.62; H, 4.39; N, 2.35.

1-(3-Bromo-4,5-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. The quinolinium iodide (5.0 g) was suspended in 50 mL of EtOH, and 1.0 g of $NaBH_4$ was added in portions with vigorous stirring. The solvent was removed in vacuo and the residue treated with 5% NH_4Cl and $CHCl_3$. The $CHCl_3$ layer was separated, dried, and evaporated to yield 3.72 g (96%) of 1-(3-bromo-4,5-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**1e**) as a yellow oil: NMR δ 2.50 (s, 3 H), 2.6–3.5 (m, 7 H), 3.63–3.95 (m, 12 H), 6.20 (s, 1 H), 6.50 (2 H), 6.95 (1 H).

Anal. Calcd for $C_{21}H_{26}BrNO_4 \cdot H_2O$: C, 55.76; H, 6.19; N, 3.10. Found: C, 56.14; H, 6.03; N, 2.93.

***N*-Allylnorlaudanosine (1c).** Allyl bromide (1.0 g) was added in drops to a stirring mixture containing 3 g of norlaudanosine **1a**, 3 g of anhydrous K_2CO_3, and 20 mL of dimethylformamide maintained at 45 °C. After stirring for 1 h the excess dimethylformamide was evaporated and the residue was taken up in 100 mL of $CHCl_3$. The $CHCl_3$ layer was washed six times with 100-mL portions of H_2O, dried, and evaporated to give 2.5 g of a pale yellow oil. Crystallization from ethanol gave a white solid, mp 80–80.5 °C. The overall yield was 90%: NMR δ 3.6 (s, 3 H), 3.8 (s, 3 H), 3.85 (s, 6 H), 5.1 (broad, 1 H), 5.3–5.4 (broad d, 2 H), 6.1 (s, 1 H), 6.6–6.8 (m, 4 H); mass spectrum, *m/e* 385 (M^+), 355, 340, 246, 233 (base peak), 206, 176, 133.

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.06; H, 7.57; N, 3.66. Found: C, 71.82; H, 7.85; N, 3.59.

1-(2-Bromo-3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (1d). This was prepared as above starting from 3,4-dimethoxyphenethylamine and 2-bromo-3-benzyloxy-4-methoxyphenylacetic acid in an overall yield of 58%: mp 101–101.5 °C; NMR δ 2.5 (s, 3 H), 3.55 (s, 3 H), 3.78 (broad s, 6 H), 5.05 (s, 2 H), 6.03 (s, 1 H), 6.63 (s, 1 H), 6.7 (s, 2 H), 7.2–7.7 (m, 5 H).

6′-Chlorolaudanosine. This was prepared as above and recrystallized from absolute ethanol: mp 130–130.5 °C (lit.[26] mp 130 °C); NMR δ 2.55 (s, 3 H), 3.65 (s, 3 H), 3.75 (s, 3 H), 3.85 (s, 3 H), 6.1 (s, 1 H), 6.55 (s, 1 H), 6.6 (s, 1 H), 6.9 (s, 1 H); mass spectrum, *m/e* 391, 248, 207, 190, 177.

1-(6-Chloro-3,4-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (7). Prepared as above, recrystallization from absolute ethanol gave a white powder: mp 152–153 °C; NMR δ 2.55 (s, 3 H), 3.7 (s, 3 H), 3.9 (s, 3 H), 5.95 (s, 2 H), 6.25 (s, 1 H), 6.6 (s, 2 H), 6.9 (s, 1 H); mass spectrum, *m/e* 375 (M^+), 337, 338, 190, 169.

Anal. Calcd for $C_{20}H_{22}ClNO_4$: C, 63.92; H, 5.80; N, 3.73; Cl, 9.44. Found: C, 63.96; H, 5.68; N, 3.27; Cl, 9.43.

Morphinandienone Synthesis. The procedure and equipment have been previously described.[2,3] It is noted that the anolyte usually consisted of ca. 100 mL of 0.5% H_2O in CH_3CN (twice distilled from P_2O_5) containing 0.1 M $LiClO_4$ and 2 g of $NaHCO_3$. Most of the $NaHCO_3$ is insoluble. The mixture is stirred with a magnetic stirring bar. In contrast to runs using Na_2CO_3, the anode usually did not "film" to any extent. After the passage of 2 F/mol at 1.1 V, the anolyte was worked up by evaporation of most of the CH_3CN and extraction with $CHCl_3/H_2O$. The crude $CHCl_3$-soluble mixture was separated by column chromatography.

The morphinandienones **2a–f** were characterized by IR, NMR, and mass spectrometry. **2a** and **2b** gave spectra superimposable on those from authentic samples.[2] Products **2c–f** have not been previously described. In each case the IR spectrum showed a characteristic set of three dienone bands with intensities decreasing in the order 1670, 1640, and 1615 cm^{-1}. The mass spectra showed the proper parent ion and M − 15 and M − 43 ions.

***N*-Allyl-*O*-methylflavinantine (2c)** was obtained as a colorless oil from the oxidation of **1c**: NMR δ 1.9 (m, 2 H), 2.65 (t, 2 H), 3.3 (m, 4 H), 3.8 (s, 3 H), 3.85 (s, 3 H), 3.9 (s, 3 H), 5.1 (broad s, 1 H), 5.3–5.4 (broad d, 2 H), 6.3 (s, 1 H), 6.4 (s, 1 H), 6.7 (s, 1 H), 6.9 (s, 1 H); UV λ_{max} (EtOH) 215, 245, 290 nm; mass spectrum, *m/e* 367 (M^+), 240, 175, 159, 145. The molecular formula was confirmed by high-resolution mass spectrometry as $C_{22}H_{25}NO_4$.

The **2′-bromo-*O*-methylflavinantine 3′-*O*-benzyl analogue 2d** was obtained as an oil from the oxidation of **1d**: NMR δ 1.95 (m, 2 H), 2.5 (s, 3 H), 3.8 (s, 3 H), 4.0 (s, 3 H), 5.05 (s, 2 H), 6.4 (s, 2 H), 7.0 (s, 1 H), 7.8–7.3 (m, 5 H); mass spectrum, *m/e* 497 (M^+), 495 (M^+), 406, 404, 331, 260, 206, 91.

Anal. Calcd for $C_{26}H_{26}BrNO_4$: C, 58.60; H, 5.27; N, 2.63. Found: C, 58.51; H, 5.23; N, 2.81.

5′-Bromo-*O*-methylflavinantine (2e) was obtained as a white solid on recrystallization from ethyl acetate/methanol: mp 214–216 °C; NMR δ 1.9 (m, 2 H), 2.45 (s, 3 H), 2.5–3.4 (m, 5 H), 3.85–3.95 (three s, 9 H), 6.35 (s, 1 H), 6.65 (s, 1 H), 8.0 (s, 1 H).

Anal. Calcd for $C_{20}H_{22}BrNO_4$: C, 57.15; H, 5.28; N, 3.33. Found: C, 56.87; H, 5.07; N, 3.26.

5′-Iodo-*O*-methylflavinantine (2f) was obtained as a white solid: mp 202–205 °C; NMR δ 1.9 (m, 2 H), 2.40 (s, 3 H), 2.5–3.4 (m, 5 H), 3.75–3.85 (three s, 9 H), 6.35 (s, 1 H), 6.65 (s, 1 H), 8.20 (s, 1 H); mass spectrum, *m/e* 467.056; mass spectrum calcd, *m/e* 467.060.

Oxidation of the 6′-Chlorolaudanosine 4′-Benzyloxy Analogue 4. The oxidation of this compound was carried out under many different conditions as described above. In all cases only cleavage products **5** and **6** were observed. A typical oxidation and isolation procedure involved oxidation of **4** (360 mg, 0.9 mmol) in the presence of Na_2CO_3 at 1.25 V at platinum for 250 min. During this period about 4 F/mol of electricity was consumed. At the end the volume of the anolyte was reduced to 15 mL, 100 mL of water was added, and the organic material was extracted with three 100-mL portions of chloroform (extract A). The aqueous layer was neutralized with 0.1 N HCl and extracted three times with 50-mL portions of chloroform (extract B). Extract A was dried and evaporated to give a pale brown gum whose TLC analysis showed the presence of four compounds besides the starting material. These compounds had R_f values of 0.0, 0.3, 0.8, and 0.9 and were separated by chromatography and identified spectroscopically.

The compound with R_f 0.9 was identified as 3,4-dimethoxy-6-chlorobenzaldehyde from spectral data: NMR δ 3.95 (s, 3 H), 4.0 (s, 3 H), 6.9 (s, 1 H), 7.4 (s, 1 H), 10.3 (s, 1 H); IR ($CHCl_3$) 1730 cm^{-1}.

The compound with R_f 0.8 was identified as *O*-methylcorypalline (**5**) from its spectral data: NMR δ 2.95 (t, 2 H), 3.15 (s, 3 H), 3.95 (s, 6 H), 6.65 (s, 1 H), 7.65 (s, 1 H); IR ($CHCl_3$) 3600–3200 (broad), 2980, 2920, 2820, 1630, 1590 cm^{-1}; mass spectrum, *m/e* 221 (M^+), 178, 163, 150 (base peak), 135, 107, 92.

The spectral and TLC properties of the compound with R_f 0.3 were identical with a known sample of *O*-methylcorypalline (**6**):[27] NMR δ 2.8 (s, 3 H), 3.9 (s, 6 H), 6.6 (s, 1 H), 6.7 (s, 1 H); mass spectrum, *m/e* 207 (M^+), 206, 190, 164 (base peak), 149 (metastable), 135, 121, 103.

Reduction of the R_f 0.0 product with sodium borohydride in ethanol gave *O*-methylcorypaldine.

Extract B was dried and evaporated to give a dirty white solid whose spectral properties corresponded to 6-chloro-3,4-dimethoxybenzoic acid: mp 86–88 °C (lit.[28] mp 85–87 °C); NMR δ 3.9 (s, 3 H), 3.95 (s, 3 H), 6.92 (s, 1 H), 7.45 (s, 1 H).

Oxidation of 7. This compound was oxidized under several conditions as described above. In a typical electrooxidation, **7** (320 mg, 0.85 mmol) was oxidized in the presence of sodium carbonate at 1.25 V at platinum for 180 min. The usual workup led to 290 mg of crude products. The TLC analysis showed the presence of four products at R_f values of 0.0, 0.3, 0.8, and 0.9. Compounds at R_f values of 0.3 and 0.8 were identified as *O*-methylcorypalline and *O*-methylcorypaldine, respectively, by comparing their spectral and TLC properties with authentic samples.

α-Hydroxy-5,4′-dimethoxy-2-methylbibenzyl. 2-Bromo-4-nitrotoluene was prepared by the method of Bunnett and Rauhut[29] and then converted on a 100-g scale to 3-bromo-4-methylaniline sulfate (127 g). 2-Bromo-4-hydroxytoluene was then produced in a standard fashion by diazotization.[30] Methylation of this phenol using 2 N NaOH and dimethyl sulfate gave 51 g of 2-bromo-4-methoxytoluene.[31]

2-Bromo-4-methoxytoluene was converted to the Grignard reagent and reacted with 3-methoxyphenylacetaldehyde as follows. In a 250-mL three-neck flask fitted with a reflux condenser, a dropping funnel, an adapter for passing in nitrogen, and a magnetic stirrer was placed 2.4 g (0.1 mol) of magnesium turnings. A mixture of 2.0 g of 2-bromo-4-methoxytoluene and 10 mL of dry ether was run into the flask. The flask was warmed until the reaction began. Stirring was started and the flask was surrounded by a dish of cold water. A mixture of 18 g of 2-bromo-4-methoxytoluene (total 20 g, 0.1 mol) and 50 ml of dry ether was added at such a rate as to cause refluxing. When the addition was complete, the mixture was stirred until the magnesium turnings disappeared. The Grignard solution was cooled in an ice bath, and 12 g (0.08 mol) of 3-methoxyphenylacetaldehyde in 30 mL of ether was added dropwise; white solid appeared near the end of the addition. The solution was stirred at room temperature for 1 h. The product was decomposed by pouring the reaction mixture into 300 g of cracked ice. A 50-mL amount of 2 N sulfuric acid was added. The ether solution was separated, and the aqueous layer was extracted with two 150-mL portions of ether. The ether solution was dried, the mixture was filtered, and the ether was removed. The product was purified by passing through an 18 × 1 in alumina column eluted by chloroform. The α-hydroxy-5,4′-dimethoxy-2-methylbibenzyl (17.5 g, 65%) was collected from fractions 12–20 (50 mL/fraction): NMR δ 2.00 (d, 1 H), 2.20 (s, 3 H), 2.90 (m, 2 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 5.18 (m, 1 H), 7.00 (m, 7 H); IR ν_{max} (neat) 3450, 1615 cm^{-1}; mass spectrum, *m/e* (% of base) 272 (10), 151 (70), 123 (100), 122 (100), 108 (50).

5,4′-Dimethoxy-2-methylbibenzyl (11). To a solution of 10 g (0.037 mol) of the α-hydroxy compound in 200 mL of dry ether and 50 mL of dry THF containing 0.5 mL of pyridine was added dropwise a solution of 10 mL of thionyl chloride in 20 mL of dry ether during 30 min with stirring. After an additional 20 min at room temperature, the reaction was cautiously quenched with cold water. Separation and evaporation of the ethereal layer gave 10 g of α-chloro-5,4′-dimethoxy-2-methylbibenzyl as a pale yellow, mobile oil. The infrared spectrum showed no OH absorption.

A solution of 2 g of this chloro compound in 10 mL of dry THF was added dropwise to a stirred solution of 600 mg of $LiAlH_4$ in 100 mL of dry THF at room temperature. After refluxing for 5 h, the reaction was cautiously quenched with wet THF. The separated aluminate was filtered off and washed with ether. The organic filtrate was washed with water, dried, and evaporated to give 1.6 g (92%) of 11 as a yellow oil: NMR δ 2.20 (s), 2.84 (s, 4 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 6.80 (m, 7 H); mass spectrum, *m/e* (% of base) 256 (35), 135 (100), 121 (21).

Anal. Calcd: C, 79.69; H, 7.81. Found: C, 79.43; H, 7.72.

Electrolysis of 5,4′-Dimethoxy-2-methylbibenzyl (11). The three-compartment cell has been described. This compound (256 mg, 1.0 mmol) was oxidized at 0 °C in 150 mL of acetonitrile with 2% water and 1 g of anhydrous Na_2CO_3. The potential was set at 1.80 V vs. $Ag/AgNO_3$. The initial current was 40 mA. The potential was pulsed to 0.0 V for 0.5 s in every 30-s period. The electrolysis was discontinued when a 3-F/mol charge had passed, which took 2.5 h. The usual workup of the anolyte solution led to a light brown residue. TLC analysis on silica gel developed with chloroform showed one component with R_f 0.15 and starting material. The component was isolated by preparative TLC and purified by preparative liquid chromatography using 40 psi of pressure with a 12 × 1 in Sephadex column. Gradient elution was performed with $CHCl_3$/1% methanol, taking 5-mL fractions. From fractions 36–40 was isolated 53 mg (22%) of compound **12** as a pale yellow solid: mp 57–59 °C; NMR δ 1.60 (s, 3 H), 2.40–3.25 (m, 4 H), 3.90 (s, 3 H, OCH_3), 6.20–7.60 (m, 6 H); IR ν_{max} ($CHCl_3$) 1665, 1630, 1625, 1600 cm^{-1}; UV (ethanol) λ_{max} (log ε) 233 (4.71), 272 (3.85) nm; mass spectrum, *m/e* (% of base) 240 (46), 225 (100).

Anal. Calcd for $C_{16}H_{16}O_2$: C, 80.00; H, 6.67. Found: C, 79.61; H, 7.00.

VOF_3 Oxidation of 11. In a 100-mL three-neck flask equipped with a calcium chloride drying tube and an inlet for passing nitrogen was placed 30 mL of CF_3COOH, 256 mg (1 mmol) of **11**, and a magnetic stirring bar. The flask was put into a benzyl alcohol–dry ice bath to keep the temperature at −14 °C, and VOF_3 (0.9 g, 7 mmol) was added. After 3 h of stirring, the mixture was poured into 60 mL of cold water containing 5 g of citric acid. The solution was basified with 5% NH_4OH and extracted with chloroform. The chloroform extracts were dried and concentrated. A compound with R_f 0.15 on silica gel developed by chloroform was isolated by preparative TLC. After purification by liquid chromatography as described above, 72 mg (30%) of a pale yellow solid with spectra identical with **12** was obtained.

Phenoxide Oxidations. All reactions were carried out in a three-compartment electrolysis cell using a stainless steel cathode, six carbon rods (0.25 × 4 in) as the anode, and a SCE of commercial design as the reference electrode. The anode potential was controlled using a PAR model 173 potentiostat. Reactions were carried out at room temperature with magnetic stirring under a nitrogen atmosphere. The solvent-supporting electrolyte solution was prepared by dissolving 5.0 g of sodium or lithium perchlorate or 7.0 g of tetraethylammonium fluoborate in 300 mL of distilled acetonitrile containing from 10 to 20 mL of H_2O. The phenoxides were prepared by reaction with 1 equiv of sodium methoxide in methanol followed by removal of the methanol or in situ by the dropwise addition of 1 equiv of NaOH in 5 mL of H_2O.

Workup consisted of removal of the acetonitrile in vacuo followed by partitioning the residue between 200 mL of chloroform and 100 mL of 10% aqueous NaOH. The organic layer was washed with saturated sodium chloride solution, dried over calcium chloride, filtered, and reduced in vacuo. Product analysis was carried out by either GLPC on a Carbowax 20 M on Chromosorb W, N.A.W. 10 ft × 0.25 in column at 250 °C or via HPLC (ALTEX) using Woelm silica gel (0.032–0.063 mm) and eluting with benzene/ethyl acetate (85:15).

1,2,10,11-Tetrahydro-6,11-dimethyl-2-oxodibenzfuran (14). *p*-Cresol (1.05 g) was oxidized at 0.25 V in the presence of 1 equiv of NaOH. After the passage of 1 F/mol, the current had dropped to 5 mA and the reaction was worked up. **13** (0.54 g) was recovered from the basic extracts, and GLPC indicated a 35% yield of **14**. The use of lithium perchlorate in place of sodium perchlorate in the above procedure gave a 37% yield of **14**. Pure **14** was obtained by passing the crude reaction mixture through a short (15 × 150 cm) silica gel column using benzene eluant followed by recrystallization from ether, mp 123 °C (lit.[22] mp 123 °C). The ^1H NMR, ^{13}C NMR, IR, and mass spectra were consistent with the proposed structure.

1,2,10,11-Tetrahydro-3,6,8,11-tetramethyl-2-oxodibenzfuran (17). 2,4-Dimethylphenol (3.75 g) was oxidized at 0.2 V in the presence of 2 equiv of NaOH. The initial current was 200 mA, and it dropped to 10 mA before completion of the reaction. The electrodes were then cleaned by wiping them with paper. Resumption of electrolysis gave an initial current of 120 mA. After the passage of 1 F/mol, the reaction was terminated and the anolyte worked up, yielding 1.97 g of $CHCl_3$-soluble material, 1.0 g of alkali-soluble material and 0.28 g of a red oil found between the $CHCl_3$ and aqueous layers. GLPC of the $CHCl_3$-soluble fraction showed the presence of 0.76 g of isohomo Pummerer's ketone (**17**), and HPLC yielded 0.74 g (20%) of this product, mp 137–139 °C (lit.[22] mp 137 °C). The ^1H NMR, ^{13}C NMR, IR, and mass spectra were consistent with the proposed structure. Minor amounts of four other unidentified compounds were also present.

1,2,10,11-Tetrahydro-4,6,7,11-tetramethyl-2-oxodibenzfuran (16). A mixture of 1.55 g of 3,4-dimethylphenol and 1.0 g of sodium methoxide in 10 mL of methanol was oxidized at 0.25 V in 200 mL of anolyte. The reaction was worked up after the passage of 1 F/mol to yield 0.77 g of 3,4-dimethylphenol and 0.45 g of crude product, which upon crystallization from ether yielded 0.24 g (31%) of homo Pummerer's ketone (**16**), mp 155 °C (lit.[22] mp 156 °C). The ^1H NMR, ^{13}C NMR, IR, and mass spectra were consistent with the proposed structure.

1,2,10,11-Tetrahydro-6,11-diethyl-2-oxodibenzfuran (18). 4-Ethylphenol was oxidized at 0.25 V and worked up after the passage of 0.3 F/mol. The ^1H NMR spectrum of the crude reaction product showed a long-range proton coupling pattern very similar to that observed in Pummerer's ketone. Integration of the NMR spectrum showed that the crude reaction mixture contained about 50% of compound **18** which was not further purified.

Oxidation of *p*-*tert*-Butylphenol. Attempts to dimerize *p*-*tert*-butylphenol under conditions similar to those used above gave only starting material and polymeric materials. This material was brown to tan in color and only slightly soluble in polar solvents. No distinct spots could be detected by TLC.

Registry No.—**2c,** 65354-46-3; **2d,** 65354-47-4; **2e,** 65354-48-5; **2f,** 65354-49-6; **4,** 65293-06-3; **5,** 6514-05-2; **6,** 16620-96-5; **7,** 65293-07-4; **11,** 61582-79-4; **12,** 36126-09-7; **14,** 546-24-7; **16,** 62156-65-4; **17,** 62156-64-3; **18,** 62224-30-0; 3-bromo-4-hydroxy-5-methoxybenzaldehyde, 2973-76-4; 3-bromo-4,5-dimethoxybenzaldehyde, 6948-30-7; 3-bromoveratryl alcohol, 52783-74-1; 3-bromoveratryl chloride,

52783-75-2; 3-bromoveratronitrile, 59116-12-0; 3-bromo-4,5-dimethoxyphenylacetic acid, 56982-10-6; 3,4-dimethoxyphenethylamine, 120-20-7; *N*-(3,4-dimethoxyphenethyl)-3-bromo-4,5-dimethoxyphenylacetamide, 65292-97-9; 1-(3-bromo-4,5-dimethoxybenzyl)-3,4-dihydro-2-methyl-6,7-methoxyisoquinolinium iodide, 65292-98-0; allyl bromide, 106-95-6; 2-bromo-3-benzyloxy-4-methoxyphenylacetic acid, 38849-42-2; 3,4-dimethoxy-6-chlorobenzaldehyde, 18083-05-5; 6-chloro-3,4-dimethoxybenzoic acid, 60032-95-3; 3-methoxyphenylacetaldehyde, 65292-99-1; α-hydroxy-5,4′-dimethoxy-2-methylbibenzyl, 65293-00-7; α-chloro-5,4′-dimethoxy-2-methylbibenzyl, 65293-01-8; 6′-chlorolaudanosine, 55954-20-6; 2-bromo-4-methoxytoluene, 36942-56-0.

References and Notes

(1) This work was supported by National Institutes of Health Grants GM19234 at Colorado State University and GM24493 at the University of Minnesota.
(2) L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Am. Chem. Soc.*, **95**, 2651 (1973).
(3) J. R. Falck, L. L. Miller, and F. R. Stermitz, *Tetrahedron*, **30**, 931 (1974).
(4) See, for example, S. M. Kupchan and A. J. Liepa, *J. Am. Chem. Soc.*, **95**, 4062 (1973).
(5) See, for example, E. Kotani, M. Kitazawa, and S. Tobinaga, *Tetrahedron*, **30**, 3027 (1974).
(6) The potentials quoted in this paper are with reference to Ag/0.1 M $AgNO_3$ in CH_3CN, except where specifically noted.
(7) L. L. Miller, F. R. Stermitz, J. Y. Becker, and V. Ramachandran, *J. Am. Chem. Soc.*, **97**, 2922 (1975).
(8) J. Y. Becker, L. L. Miller, and F. R. Stermitz, *J. Electroanal. Chem. Interfacial Electrochem.*, **68**, 181 (1976).
(9) An alternative solvent system has been reported: E. Kotani and S. Tobinaga, *Tetrahedron Lett.*, 4759 (1973).
(10) S. M. Kupchan and C. Kim, *J. Am. Chem. Soc.*, **97**, 5624 (1975).
(11) M. A. Schwartz and J. S. Mami, *J. Am. Chem. Soc.*, **97**, 1239 (1975).
(12) E. A. Mayeda, L. L. Miller, and J. F. Wolf, *J. Am. Chem. Soc.*, **94**, 6812 (1972).
(13) K. L. Stuart, *Chem. Rev.*, **71**, 41 (1971).
(14) J. R. Falck, L. L. Miller, and F. R. Stermitz, *J. Am. Chem. Soc.*, **96**, 2981 (1974).
(15) S. M. Kupchan, V. Kameswaran, J. T. Lynn, D. K. Williams, and A. J. Liepa, *J. Am. Chem. Soc.*, **97**, 5622 (1975).
(16) See, for example, w. Nagata, T. Terasawa, and T. Sugasawa, Japan Patent 7 034 813; *Chem. Abstr.*, **74**, 87685 (1971).
(17) R. T. Blickenstaff, A. C. Ghosh, and G. C. Wolf, "Total Synthesis of Steroids", Academic Press, New York, N.Y., p 194.
(18) A. Ronlan, O. Hammerich, and V. D. Parker, *J. Am. Chem. Soc.*, **95**, 7132 (1973).
(19) W. I. Taylor and A. R. Battersby in "Oxidative Coupling of Phenols", Marcel Dekker, New York, N.Y., 1967.
(20) J. M. Bobbitt, I. Noguchi, H. Yagi, and K. H. Weisgraber, *J. Org. Chem.*, **41**, 845 (1976).
(21) E. Adler, L. Junghahn, U. Lindberg, B. Berggren, and G. Westin, *Acta Chem. Scand.*, **14**, 1261 (1960).
(22) T. C. Bruice, M. J. Gregory, and S. L. Walters, *J. Am. Chem. Soc.*, **90**, 1612 (1968).
(23) C. G. Haynes, A. H. Turner, and A. Waters, *J. Chem. Soc.*, 2823 (1956).
(24) A. Nilsson, A. Ronlan, and V. D. Parker, *J. Chem. Soc., Perkin Trans 1*, 2338 (1973).
(25) A. Ronlan, private communication.
(26) C. Y. Hopkins and M. J. Chisholm, *Can. J. Res., Sect. B*, **24**, 208 (1946).
(27) Y. Inubushi, Y. Aoyagi, and M. Matsuo, *Tetrahedron Lett.*, 2363 (1970).
(28) L. C. Raiford and D. E. Floyd, *J. Org. Chem.*, **8**, 358 (1943).
(29) J. F. Bunnett and M. M. Rauhut, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 160.
(30) S. A. Mahood and P. V. L. Schaffner, ref 29.
(31) H. E. Ungade and E. F. Orwell, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1953, p 130.

Methano-Bridged 14π-Electron Aromatic Annulenes. 1. 1,6-Methanofluorenyl and 9-Methyl-1,6-methanofluorenyl Anions

Ronald J. Hunadi[1] and George K. Helmkamp*

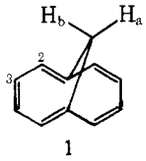
Department of Chemistry, University of California, Riverside, California 92521

Received September 2, 1977

The syntheses of 1,6-methanofluorene, *syn*- and *anti*-9-methyl-1,6-methanofluorene, and their monoanions are described. The anions were shown by proton NMR to be delocalized aromatic systems existing in "cycloheptatriene" rather than "norcaradiene" forms.

Several methano-bridged 14π-electron aromatic systems have been described, namely *syn*-1,6-methano-8,13-oxido[14]annulene,[2] *syn*-1,6-methano-8,13-bismethano[14]-annulene,[3] 3,4-benzo-1,6-methano[10]annulene,[4] 1,7-methanododecapentaenyl dianion,[5] 1,6-methanododecapentaenyl dianion,[5] the dianion of 1-aza-2-methoxy-5,10-methano[12]annulene,[6] 2,3-benzo-1,6-methano[10]annulene,[7] and the 1,6-methanocarbazoyl anion.[8] Proton NMR spectroscopy showed delocalized aromatic π systems for all of these except the [11]annulene dianion, which decomposed before a spectrum could be recorded. In our initiation of a study of the effects of methano bridges on the physiological properties of psychoactive compounds (via reduction in aromaticity and alteration of steric factors) we found it necessary to investigate bridging procedures for various types of similar parent species. Included among them was fluorene, which can be considered a benzoannelated indene.

Benzoannelation reduces aromaticity of a molecule and its diamagnetic ring current. For example, Vogel[7] showed such a reduction for 2,3 annelation of 1,6-methanonaphthalene, **1**, with the observation that resonance signals for protons H_a and H_b are shifted 0.5 and 1.9 ppm, respectively, downfield on introduction of the additional ring.



1

We now wish to report the syntheses of 1,6-methanofluorene (**2**) and 9-methyl-1,6-methanofluorene (**3**), and their corresponding anions **4** and **5**. The anions exhibited electron delocalization over the entire π system, but a decided downfield shift of bridge protons relative to those in the methanoindenyl anion[9] indicated a reduced diamagnetic ring current due to the additional ring.[10]

The key intermediate for the synthesis of 1,6-methanofluorene,[11] **2**, was ketone **6**, whose preparation from indene was already described.[13] It was readily reduced to the epimeric alcohols, **7**, which then were converted successively to the bridged *syn*-alcohol **8**, mesylate **9**, and mixture of elimination products **10** and **11**.

Previous experience showed that **10** should be preferred for the conversion to diene **2**. Since the **10**/**11** ratio from mesylate **9** was 60:40 (somewhat more favorable after chromatography

0022-3263/78/1943-1586$01.00/0