of f_i and the value of Δ^0. The least-squares criteria minimized the $\sum(\nu_{ij(obsd)} - \nu_{ij(calcd)})^2$ for all data for a given substrate–shift reagent set for a given type of nucleus ^1H or ^{13}C; we used the computer program GENLSS.[28]

The results are summarized in Tables 6-1(a) through 6-1(f) of ref 24.

The scalar errors of the slopes are nearly constant for a given data set. In carrying out the minimization which gave the data in the tables, the scalar error in the directly observed shift data, the ν_{ij} values were minimized. This does not automatically result in scalar errors for the Δ_i. Some authors have used relative errors for the Δ_{ij};[25] this may have been the correct choice but hardly for the reasons advanced. The form of error distribution can readily be ascertained by standard techniques.

There is a close correspondence between the scalar standard deviations of the observed shift values, the first number listed (based on GENLSS runs), and the scalar standard deviations of the calculated shift values, the second number (based on the data in Table I): for Bz-Pro-OCH_3 and Eu (0.13, 0.11), Yb–^1H (0.1, 0.25), and Yb–^{13}C (0.5, 0.4); for Ac-Pro-OCH_3 and Eu (0.15, 0.09), Yb–^1H (0.24, 0.16) and Yb–^{13}C (0.23, 0.3).

Computations. Least-squares evaluations of Δ_i were performed by use of GENLSS.[28] Figures 1 and 2 were prepared by ORTEP.[29] Molecular mechanics computations utilized MOLMEC[30] and the force field previously described.[2]

Acknowledgment. This work was supported in part by U.S. Energy Research and Development Administration contract No. (40-1)-2690 with the Institute of Molecular Biophysics. We are also grateful to the Computing Advisory Committee for a grant of computing time which made this work possible.

Registry No. Ac-Pro-OCH_3, 27460-51-1; Bz-Pro-OCH_3, 5493-38-9; acetic anhydride, 108-24-7; proline, 147-85-3; H-Pro-OCH_3, 2577-48-2.

Supplementary Material Available: Observed and calculated ^1H and ^{13}C shift values for *S-trans*-Bz-Pro-OCH_3 and for *S-trans*-Ac-Pro-OCH_3 (5 pages). Ordering information is given on any current masthead page.

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(30) D. F. DeTar, *Comput. Chem.*, 1, 141 (1977).

Regiospecific Electroacetoxylation of 4-Methylphenyl Acetate to Form 4-Acetoxybenzyl Acetate. A Significant Procedure for Vanillin Synthesis Involving Novel Etherification Methods of Aryl Bromides

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Received January 23, 1979

Electroacetoxylation of 4-methylphenyl acetate (1) was carried out in AcOH–*t*-BuOH (9:1 v/v) in in the presence of copper(II) acetate by using carbon electrodes to give the side-chain-oxidized products in 88% selectivity (90% conversion), i.e., 4-acetoxybenzyl acetate (**2a**, 69%), 4-acetoxybenzaldehyde (**4a**, 8%), and 4-acetoxybenzylidene diacetate (**3**, 3%). The electrolysis products **2a**, **3**, and **4a**, either by platinum oxide catalyzed oxygen oxidation or by acid-catalyzed hydrolysis, were smoothly converted to 4-hydroxybenzaldehyde (**4b**) whose bromination provided 3-bromo-4-hydroxybenzaldehyde (**5a**, 90%) as well as 3,5-dibromo-4-hydroxybenzaldehyde (**5b**, 4.5%). Treatment of **5a** with either ROH–NaOH–CaO/DMF–$CuCl_2$ or ROH–BaO–DMF–$CuCl_2$ resulted in vanillin (**6a**, 94%) and ethyl vanillin (**6b**, 93%), respectively. On the other hand, acid-catalyzed hydrolysis of **2a** gave 4-hydroxybenzyl alcohol (**11**, 89%), and acid-catalyzed alcoholysis of **2a** furnished 4-hydroxybenzyl ethers **8a** (100%) and **8b** (99%). The oxygen oxidation of both **8** and **11** can produce **4b** in good yield. 4-Hydroxy-3-methoxy(or ethoxy)benzyl ether (**10**), another key precursor for the vanillin synthesis, was prepared from both **8** and **11** by bromination followed by etherification with ROH–BaO–DMF–$CuCl_2$ in good yield.

Our interest in the electrolytic side-chain oxidation of 4-cresol homologues was stimulated by the good results obtained from the chemical oxidation of 2,6-dialkyl-4-methylphenols into the corresponding 3,5-dialkyl-4-hydroxybenzaldehydes.[1] Basically, if the preparation of 4-hydroxybenzyl alcohol (**11**) and/or 4-hydroxybenzaldehyde (**4b**) could be accomplished by electrochemical oxidation of 4-cresol, the procedure would be of remarkable utility since the oxidized products can be widely used as important chemicals in the organochemical industry.

The lack of the regioselectivity in the anodic oxidation of nonmasked phenols[2] enables us to choose 4-methylphenyl acetate (**1**) for our present work. However, some patents on the chemistry of the catalytic oxygen oxidation of 1[3] reveal that the conversion of **1** into **4a** (Y = Ac) has been shown to occur with less than 31% selectivity (ca. 63% conversion). Our aim, based on electroacetoxylation of the methyl group of **1**, was to generate 4-acetoxybenzyl acetate (**2a**), prior to the formation of **4b**. Additionally, we examined several approaches to vanillins (**6**) from the acetate **2a** as outlined in Schemes I and II, which involve novel alkoxylation reactions of 2-bromophenols **5**, **9**, and **12**.

Electroacetoxylation of 4-Methylphenyl Acetate (1). The anodic side-chain acetoxylation of aromatic compounds has been carried out in a variety of solvent-supporting electrolyte-additive systems: AcOH–Ac_2O–AcO-Na,[4] AcOH–AcOK–Co^{2+},[5] AcOH–Me_4NOTs,[6] AcOH–

(1) (a) Orlando, C. M., Jr. *J. Org. Chem.* **1970**, *35*, 3714. (b) Cohen, L. A. *Ibid.* **1957**, *22*, 1333. (c) Becker, H. D. *Ibid.* **1965**, *30*, 982. (d) Nishinaga, A.; Itahara, T.; Matsuura, T. *Angew. Chem.* **1975**, *87*, 386; *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 356.

(2) (a) Fichter, F.; Ackermann, F. *Helv. Chim. Acta* **1919**, *2*, 583. (b) Nilsson, A.; Palmquist, U.; Pettersson, T.; Ronlán, A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 696.

(3) (a) Kato, T.; Iwasaki, H.; Yoshida, K. Japananese Patent 75 35 066, 1975; *Chem. Abstr.* **1976**, *85*, 5360. (b) Bashkirov, A. N.; Vygodskaya, I. U.; Grozhan, M. M.; Lapitskii, Yu. A.; Pokrovskaya, E. G.; Kamzolkin, V. V. British Patent 1 403 873, 1975; *Chem. Abstr.* **1975**, *83*, 178596.

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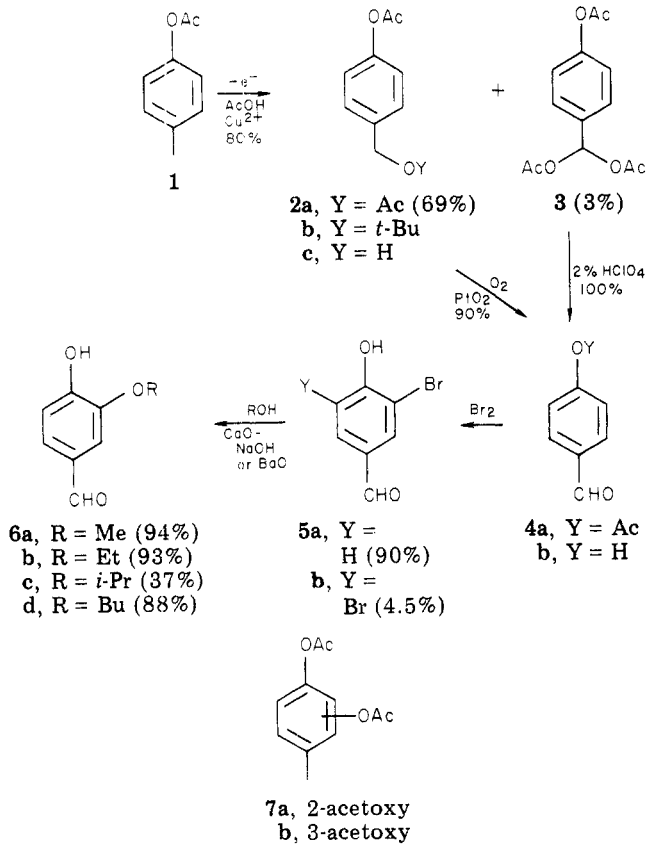
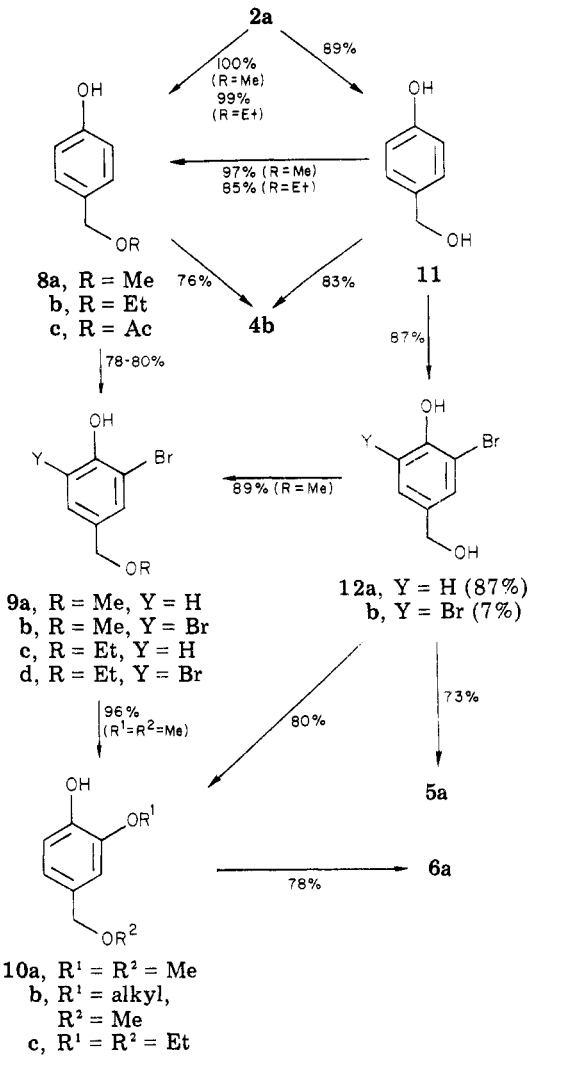
Scheme I



Scheme II



Me_4NOTs–AcOK,[6] AcOH–Me_4NNO_3,[6,7] and AcOH–Me_4NNO_3–AcOK.[6] In general, the electroacetoxylation of alkylbenzenes yields mixtures of both side-chain and ring-substituted acetates as well as other byproducts.[6] The relatively weak electron-donating character of the acetoxy group of 1 led us to anticipate some difficulties in searching for the desirable electrolysis conditions. Nevertheless, we attempted to elucidate influential factors for both the conversion yield and the product selectivity and examined some preliminary electrolyses of 1 under the conditions shown in Table I.

Electrolysis carried out on 1 with Et_4NOTs (entry 3), in contrast to AcONa[8] or Et_3N (entries 1 and 2),[9] provided regiospecific results in producing 2, indicating that the formation of most of the ring-substituted compounds could be suppressed under the conditions in entry 3. For enhancement of the total yield of the side-chain-oxidized products, addition of metal acetate additives appeared promising since yields were almost doubled by adding 0.24–0.17 molar equiv of the metal acetates for 1 in the electrolysis solution (entries 4–8), and the use of carbon

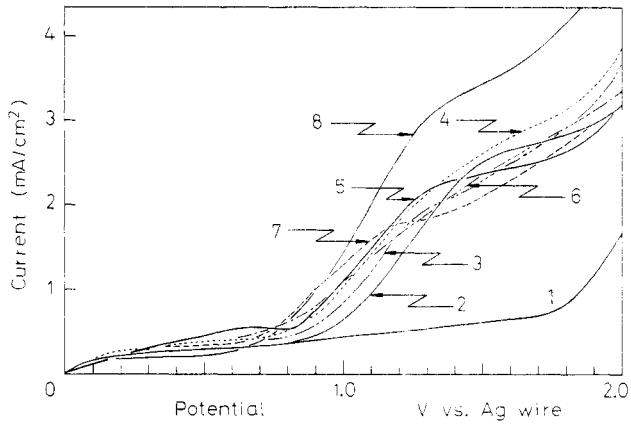


Figure 1. Current–potential curves for 1 (1 mmol) in AcOH (10 mL) with various metal acetates. The measurements were carried out at 18 °C, with Et_4NOTs (920 mg) as a supporting electrolyte and Pt electrodes (1.5 × 2.0 cm^2). All potentials were measured vs. a Ag wire: (1) background, AcOH–Et_4NOTs; (2) 1 in AcOH–Et_4NOTs; (3) $Co(OAc)_2$ (0.243 mmol); (4) $Ce(OAc)_3$ (0.222 mmol); (5) $Cu(OAc)_2·H_2O$ (0.221 mmol); (6) $Mn(OAc)_2·4H_2O$ (0.171 mmol); (7) $Pb(OAc)_2·3H_2O$ (0.171 mmol); (8) $Fe(OAc)_2OH$ (0.211 mmol).

(4) Eberson, L. *J. Am. Chem. Soc.* **1967**, *89*, 4669.
(5) Koehl, W. J., Jr. U.S. Patent 3448021, 1969; *Chem. Abstr.* **1969**, *71*, 49605.
(6) Ross, S. D.; Finkelstein, M.; Petersen, R. C. *J. Org. Chem.* **1970**, *35*, 781.
(7) Ross, S. D.; Finkelstein, M.; Petersen, R. C. *J. Am. Chem. Soc.* **1967**, *89*, 4088.
(8) According to Eberson's anodic acetoxylation, the electrolysis of 4-methylanisole in AcOH–AcONa–Ac_2O has been shown to give 4-methoxybenzyl acetate b as a major product; see ref 4.
(9) In contrast to the result (Table I, entry 2), the electrolysis of 4-methylanisole (a, 0.806 mmol) in AcOH (10 mL)–Et_3N (1 mL) [Pt electrodes (3 cm^2), 15–19 °C, 4 V (14-8 mA/cm^2, 4 F/mol)] gave b (54%) as a major product as well as c (16%), d (13%), and e (6%).

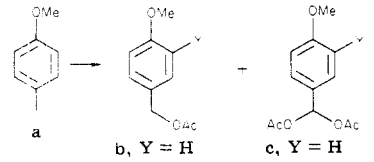


Table I. Conditions[a] and Results of Electroacetoxylation of 4-Methylphenyl Acetate (1)

entry	solvent	supporting electrolyte	additive	applied voltage, V (current, mA)	% conversion	side-chain oxidized products	product selectivity, % 2a	3	4a	2b	7a	7b	others[e]
1	AcOH	AcONa		6.8–7.0 (50)	50	24	24				17	5	54
2	AcOH	Et_3N		8.0–9.1 (100)[b]	61	25	25				15	5	52
3	AcOH	Et_4NOTs		8.0–9.1 (50)	74	34	34						27
4	AcOH	Et_4NOTs	$Mn(OAc)_2 \cdot 4H_2O$	6.0–7.0 (60)[c]	64	42	26	trace	16				
5	AcOH	Et_4NOTs	$Cu(OAc)_2 \cdot H_2O$	9.0–11.0 (60)[c]	54	53	46	trace	7				24
6	AcOH	Et_4NOTs	$Co(OAc)_2$	10.0–12.0 (60)[c]	72	49	41	trace	8				22
7	AcOH	Et_4NOTs	$Pb(OAc)_2 \cdot 3H_2O$	9.0–12.0 (60)[c]	60	57	48	trace	9				23
8	AcOH	Et_4NOTs	$Ce(OAc)_3$	9.0–10.0 (60)[c]	64	58	47	2	9				28
9	AcOH	Et_4NOTs	$Cu(OAc)_2 \cdot H_2O$	7.0–8.0 (60)	100	60	47	8	5				19
10	AcOH	Et_4NOTs	$Cu(OAc)_2 \cdot H_2O$	2.0–4.5 (30)[d]	76	68	62		6				20
11	AcOH-*t*-BuOH (9:1)	Et_4NOTs	$Fe(OAc)_2OH$	5.2–5.4 (30)	96	71	56	5	10	trace			16
12	AcOH-*t*-BuOH (9:1)	Et_4NOTs	$Cu(OAc)_2 \cdot H_2O$	5.7–6.0 (30)	90	88	76	3	9	trace			11
13	AcOH-*t*-BuOH (7:3)	Et_4NOTs	$Cu(OAc)_2 \cdot H_2O$	5.9–6.3 (30)	78	93	70	4	14	5			8
14	AcOH-*t*-BuOH (6:4)	Et_4NOTs	$Cu(OAc)_2 \cdot H_2O$	6.1–6.8 (30)	87	83	59	4	16	4			10

[a] The electrolyses were carried out at 17–30 °C with two carbon-plate electrodes and terminated after passage of 10 F/mol of electricity. [b] 20 F/mol of electricity was passed. [c] Platinum electrodes (3 cm^2) were used. [d] Carried out at 39–44 °C. [e] Based on the weight of isolated other products.

electrodes improved the conversion yield strikingly in contrast to that of platinum electrodes (entries 5 and 9). To our surprise, the cosolvent of AcOH–*t*-BuOH for the electrolysis resulted in an 83–93% yield of side-chain-oxidized products **2a**, **3**, and **4a** (entries 12–14).

The current–potential curves of **1** in the presence of metal acetates in Et_4NOTs–AcOH are shown in Figure 1. In the absence of the additive, the current began to pass at 0.90–0.95 V (vs. Ag wire). After addition of $Cu(OAc)_2$, the anodic limit shifted to 0.75–0.80 V (vs. Ag wire). Similar effects of metal acetates were observed in most cases. These results suggest that the presence of the metal acetate additive facilitates electron transfer from the substrate to the anode on account of a decrease of the oxidation potential of **1**. Furthermore, increasing total yields of the side-chain-oxidized products are felt to be due, in part, to the effect of the additive, i.e., paramagnetic monomeric copper(II) species,[10] in promoting smooth oxidation of the benzyl radical into the benzyl cation intermediate. On the other hand, addition of *t*-BuOH in the electrolysis solution did not give any different current–potential curve for **1**. At present, one can only speculate about positive contributions of *t*-BuOH to the fate of the unstable intermediate derived from discharge of the substrate at the vicinage of the anode.

Hydrolysis and Alcoholysis of 2a and 12a. Both base-[11] and acid-catalyzed alcoholysis of **2a** afforded **8**. Similarly, the acid-catalyzed alcoholysis of **12a** afforded **9a** (89%). However, complete hydrolysis of **2a** in aqueous alkaline media failed to give complex materials. Successfully, we found that the hydrolysis of **2a** in aqueous $HClO_4$–THF at 50–60 °C furnished the desired **11** (89%).

Preparation of 4-Hydroxybenzaldehyde (4b) from 2a, 3, 8a, or 11. The PtO_2-catalyzed oxygen oxidation of **11** in aqueous 40% glyme afforded **4b**.[12] Similarly, oxidation of **12a** gave **5a** in good yield. The PtO_2–O_2 oxidation of **2a** and **8a** into **4b** in aqueous 1% $HClO_4$–THF was also accomplished. Independently, hydrolysis of **3** in aqueous 2% $HClO_4$–THF also gave **4b** in a quantitative yield.

Bromination of 4b, 8, and 11, Giving 5, 9, and 12. Treatment of **4b** with Br_2–$CHCl_3$[13] gave **5a** (90%) and **5b** (4.5%). Similarly, treatment of **8a** gave **9a** (R = Me, Y = H, 78%) and **9b** (R = Me, Y = Br, 8%). However, the same treatment of **11** at room temperature provided a 4:1 mixture of **12a** and **12b** together with byproducts. In order to improve the yield of **12a**, we treated a mixture of **11** and $CaCO_3$ in ethanol with Br_2–EtOH at −5–3 °C for 5 h, giving **12a** (Y = H, 87%) and **12b** (Y = Br, 7%).

Conversion of Aryl Bromides into Alkyl Aryl Ethers. To accomplish our overall goal of the preparation of vanillins (**6**) and their precursors **10**, we explored the novel and practical substitution reaction of the bromides **5**, **9**, and **12** with alkoxylate, giving the corresponding alkyl aryl ethers **6** and **10**. In 1969, Bacon and Rennison reported an efficient copper(I) iodide assisted synthesis of alkyl aryl ethers from the appropriate aryl halides using sodium alcoholate in alcoholic 2,4,6-collidine.[14] More recently, Baldwin and Gates have found that methoxylation of 4-*tert*-butyl-2,6-dibromophenol with MeOH–MeONa–DMF–CuI gives the corresponding ether in 89% yield.[15]

(10) Kochi, J. K.; Subramanian, R. V. *J. Am. Chem. Soc.* **1965**, *87*, 4855.
(11) Hayashi, H.; Oka, S. *Bull. Inst. Chem. Res., Kyoto Univ.* **1974**, *52*, 514.
(12) Heyns, K.; Blazejewicz, L. *Tetrahedron* **1960**, *9*, 67.
(13) Smith, L. I. "Organic Synthesis", Collect. Vol. II; Wiley: New York, N.Y., 1943; p 95.
(14) Bacon, R. G. R.; Rennison, S. C. *J. Chem. Soc. C* **1969**, 312.

Table II. Etherification of Aryl Bromides with ROH-NaOH-CaO/DMF-$CuCl_2$ or ROH-BaO-DMF-$CuCl_2$

entry	aryl bromide	ROH, R =	reagent	ArOR	% isolated yield	ArH	recvrd aryl bromide	others
1	5a	Me	NaOH-CaO	6a	94			
2	5a	Me	BaO	6a	94			
3	5a	Me	MeONa	6a	96			
4	5a	Et	NaOH-CaO	6b	16	25	25	
5	5a	Et	BaO	6b	93			
6	5a	Et	EtONa	6b	9	66		21[a]
7	5a	*i*-Pr	BaO	6c	37			
8	5a	Bu	BaO	6d	88			
9	9a	Me	NaOH-CaO	10a	96			
10	9a	Me	BaO	10a	94			
11	9a	Et	BaO	10b (R^1 = Et)	92			
12	9a	*i*-Pr	BaO	10b (R^1 = *i*-Pr)	83			
13	9a	Bu	BaO	10b (R^1 = Bu)	94			
14	2-bromophenol	Me	BaO	2-methoxyphenol	98			
15	4-bromophenol	Me	BaO	4-methoxyphenol	24		71	

[a] 8b was obtained as a reduced product.

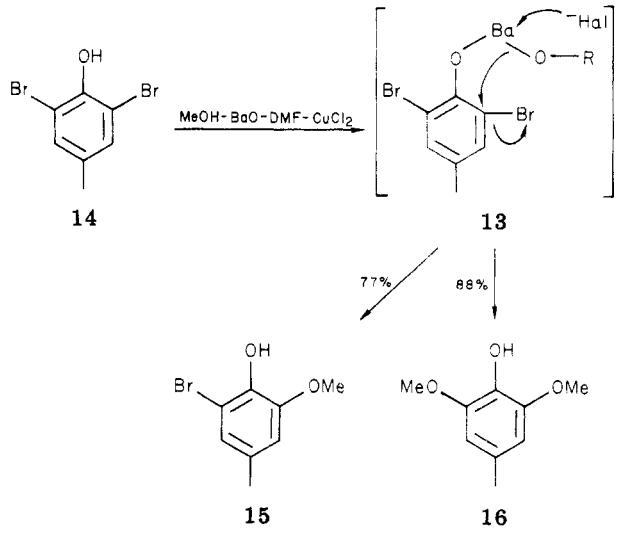
In order to develop a highly convenient procedure without using expensive sodium alcoholates, we examined the utility of alkali-alcohol solutions prepared by refluxing a mixed solution of ROH-NaOH-CaO, expecting the formation of alkoxylate in situ, and have found that the solutions can be used for our present purpose. Thus, treatment of **5a** with MeOH-NaOH-CaO-DMF in the presence of copper(II) chloride afforded **6a** (entry 1, Table II) in accordance with the case of MeOH-MeONa-DMF-$CuCl_2$, giving **6a** (entry 3). However, inferior results were obtained on the ethyl vanillin synthesis (Table II, entries 4 and 6).

A more versatile procedure for the preparation of alkyl aryl ethers from 2-halogenophenols was found, since the reaction of **5a** with EtOH-BaO-DMF-$CuCl_2$ did take place at 110 °C when the solvents were slowly removed, giving **6b** in 93% yield (entry 5, Table II). To demonstrate the generality of the barium oxide method, we synthesized a variety of alkyl ethers **6** (R = alkyl) and **10** (R^1 = alkyl, R^2 = Me). The results of these reactions are shown in Table II (entries 2, 7, 8, 10–13).

In an attempt to elucidate the scope of this interesting reaction, we have examined the reactivity of several aryl bromides with the reagent and found that, in most cases, the replacement of the bromine atom of 2-bromo- and/or 2,6-dibromophenols can smoothly proceed, in contrast to the case for 4-bromophenol (entries 14 and 15). It should be also noted that the reactions of 2-bromoanisole, 2-bromoaniline, and 4-bromotoluene with the barium oxide solution failed. All of these data tend to indicate that this replacement proceeded through a barium salt intermediate **13** which would facilitate the intramolecular exchange reaction of the bromine atom with alkoxy group (Scheme III).

On the basis of the above assumption, we carried out monomethoxylation of 2,6-dibromo-4-methylphenol (**14**) by using the barium oxide reagent. The barium salt **13** free from the solvent was treated with $CuCl_2$-DMF to give **15** (77%) along with **16** (3%). In contrast, treatment of **14** with MeOH-BaO-DMF-$CuCl_2$ with repeated removal and addition of MeOH every 2 h led successfully to **16**.

Scheme III



Experimental Section

IR spectra were recorded on a JASCO IRA-1 grating spectrometer. ^1H NMR spectra were determined at 60 MHz with a Hitachi R-24 spectrometer. Chemical shifts are quoted in parts per million downfield from Me_4Si used as an internal reference. Melting and boiling points are uncorrected. Elemental analyses were performed in our laboratory. Commercially available **4b**, **6a**, and **6b** were used as authentic samples in identification.

Electrolytic Acetoxylation of 4-Methylphenyl Acetate (1). A mixture of 1 (105 mg, 0.70 mmol), Et_4NOTs (923 mg), $Cu(OAc)_2 \cdot H_2O$ (45.3 mg), and *t*-BuOH (1 mL) in AcOH (9 mL) was electrolyzed in an undivided cell under a constant current of 30 mA, 5.7–6.0 V, for 6.25 h at room temperature. The current direction was changed at every 0.5 min by a commutator. After being concentrated, the residue was taken up in ether and washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The residual oil was treated with Ac_2O (100 mg) and pyridine (20 mg) for 2 h. The mixture was worked up in the usual manner to give **2a**[11] (100 mg, 69%), **3** (5 mg, 3%), and **4a**[16] (9.6 mg, 8%), as well as recovered 1 (10.4 mg, 10%), after chromatography (SiO_2, benzene–hexane–AcOEt, 10:10:1).

4-Acetoxybenzylidene Diacetate (3): bp 129–131 °C (0.008 mm); IR (neat) 1760, 1615, 1509, 1373 cm^{-1}; NMR (CCl_4) δ 2.11 (s, 6, CH_3CO_2), 2.29 (s, 3, CH_3CO_2Ar), 7.10 (d, 2, J = 9.6 Hz, ArH), 7.48 (d, 2, J = 9.6 Hz, ArH), 7.62 (s, 1, OCHO). Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.65; H, 5.30. Found: C, 58.78; H, 5.21.

Various electrolysis conditions and results are indicated in Table I.

4-Hydroxybenzaldehyde (4b) from 2a. A solution of **2a** (65.0 mg, 0.311 mmol), aqueous 1% $HClO_4$ (2 mL), and PtO_2 (23 mg,

(15) Baldwin, D.; Gates, P. S. German Offen. 2627874, 1977; *Chem. Abstr.* **1977**, *86*, 171074.

(16) Papadakis, P. E. *J. Am. Chem. Soc.* **1945**, *67*, 1799.

0.101 mmol) in THF (1 mL) under oxygen was vigorously stirred at 50–60 °C for 16 h. After 3.5 mL of oxygen was consumed, the mixture was diluted with acetone, and the organic layer was worked up to give **4b** (34.0 mg, 90%).

Similarly, **4b** was obtained in quantitative yield from **3** on treatment with aqueous 2% $HClO_4$ in THF at 45–50 °C for 12 h.

Oxidation of **11** with oxygen, using PtO_2 in aqueous 40% glyme at room temperature, also gave **4b**. **4b** was independently obtained in 76% yield from **8a** on treatment with $HClO_4$ and PtO_2, and the oxidation of **10a** gave **6a** in 78% yield.

3-Bromo-4-hydroxybenzaldehyde (5a, Y = H) from 4b. To a stirred solution of **4b** (245 mg, 2.00 mmol) in $CHCl_3$ (5 mL) was added dropwise a mixed solution of Br_2 (0.11 mL, 2.1 mmol) and $CHCl_3$ (2 mL), and the mixture was stirred for 0.5 h at room temperature and for 1 h at 40 °C. After the reaction was quenched with aqueous $NaHCO_3$, the organic layer was worked up to give a mixture of **5a**[17] (90%) and **5b**[17] (Y = Br, 4.5%). Similarly, **5a** was obtained in 73% yield by oxidation of **12a**.

Vanillin (6a, R = Me) from 5a. Procedure A. To a solution obtained by refluxing a mixture of NaOH (335 mg, 7.80 mmol) and CaO (1.11 g, 19.8 mmol) in MeOH (5 mL) for 7 h under N_2 was added a mixture of **5a** (88.2 mg, 0.439 mmol) and $CuCl_2$ (28 mg, 0.208 mmol) in DMF (2 mL). The mixture was stirred for 3 h at ca. 110 °C. After removal of most of the solvent under reduced pressure at ca. 110 °C, the residue was poured into aqueous 5% HCl. The organic layer was extracted with ether and worked up in the usual manner to give **6a** (62.8 mg, 94%), after chromatography (Table II, entry 1). Similarly, etherifications of the compounds **5a** (R = Et) and **9a** (R = Me) were carried out and the results are shown in entries 4 and 9.

Procedure B. To a suspension of BaO (520 mg, 3.40 mmol) in MeOH (3 mL) under N_2 was added a mixture of **5a** (93.0 mg, 0.463 mmol) and $CuCl_2$ (29 mg, 0.216 mmol) in DMF (2 mL). The mixture was stirred for 3 h at 115 °C and then most of the solvents were removed under reduced pressure. The residue was taken up in MeOH, and the insoluble materials were separated by centrifugation. The organic layer was worked up in the usual manner to give **6a** (65.9 mg, 94%, Table II, entry 2). Similarly, etherifications of the compounds **5a** (R = Et, *i*-Pr, Bu) and **9a** (R = Me, Et, *i*-Pr, Bu) as well as 2- and 4-bromophenol were carried out, and the results are shown in entries 5, 7, 8, and 10–15.

Isopropyl Vanillin (6c, R = *i*-Pr): bp 74–76 °C (0.02 mm); IR (neat) 3364 (OH), 1680, 1595, 1512, 1390, 1379 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (d, 6, CH_3), 4.35–4.92 (m, 1, CH), 6.57 (br s, 1, OH), 7.01 (d, 1, J = 11.2 Hz, ArH), 7.39 (dd, 1, J = 11.2, 2.4 Hz, ArH), 7.41 (d, 1, J = 2.4 Hz, ArH), 9.79 (s, 1, CHO). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.62; H, 6.80.

Butyl Vanillin (6d, R = Bu): bp 75–78 °C (0.015 mm); IR (neat) 3350 (OH), 1678, 1594, 1510 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (t, 3, CH_3), 1.18–2.19 (m, 4, CH_2), 4.11 (t, 2, CH_2O), 6.57 (br s, 1, OH), 7.02 (d, 1, J = 11.2 Hz, ArH), 7.41 (dd, 1, J = 11.2, 2.4 Hz, ArH), 7.42 (d, 1, J = 2.4 Hz, ArH), 9.80 (s, 1, CHO). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.97; H, 7.26.

2-Ethoxy-4-(methoxymethyl)phenol (10b, R^1 = Et): bp 112–115 °C (3 mm); IR (neat) 3390 (OH), 1607, 1514 cm^{-1}; NMR ($CDCl_3$) δ 1.41 (t, 3, CH_3), 3.34 (s, 3, CH_3O), 4.10 (q, 2, CH_2O), 4.34 (s, 2, CH_2), 5.73 (br s, 1, OH), 6.78–6.99 (m, 3, ArH). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 66.16; H, 7.80.

2-Isopropoxy-4-(methoxymethyl)phenol (10b, R^1 = *i*-Pr): bp 64–66 °C (0.008 mm); IR (neat) 3397 (OH), 1604, 1511 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (d, 6, CH_3), 3.35 (s, 3, CH_3O), 4.35 (s, 2, CH_2), 4.23–4.77 (m, 1, CHO), 5.95 (br s, 1, OH), 6.85 (m, 3, ArH). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.29; H, 8.21.

2-Butoxy-4-(methoxymethyl)phenol (10b, R^1 = Bu): bp 80–82 °C (0.01 mm); IR (neat) 3403 (OH), 1608, 1516 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (t, 3, CH_3), 1.14–2.08 (m, 4, CH_2), 3.34 (s, 3, CH_3O), 4.04 (t, 2, CH_2O), 4.36 (s, 2, CH_2), 5.72 (broad s, 1, OH), 6.84 (m, 3, ArH). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.40; H, 8.61.

Similarly, **2-ethoxy-4-(ethoxymethyl)phenol (10c, R^1 = R^2 = Et)** was prepared from **9c** in 96% yield: bp 125–127 °C (3 mm); IR (neat) 3400 (OH), 1611, 1514 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, 3, CH_3), 1.42 (t, 3, CH_3), 3.50 (q, 2, CH_2O), 4.12 (q, 2, CH_2O), 4.41 (s, 2, CH_2), 5.73 (br s, 1, OH), 6.78–7.02 (m, 3, ArH). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.32; H, 8.42.

Procedure C. To a solution of MeONa (6.08 mmol) in MeOH (5 mL) under N_2 was added a mixture of **5a** (109 mg, 0.542 mmol) and $CuCl_2$ (25 mg, 0.186 mmol) in DMF (2 mL). The mixture was stirred for 3 h at ca. 115 °C and worked up in the same manner as described above, giving **6a** (78.7 mg, 96%, Table II, entry 3). Similarly, etherification of **5a** (R = Et) was carried out and the result is shown in entry 6.

Similarly, **10a** was also obtained in 80% yield from **12a**.

4-(Methoxymethyl)phenol (8a, R = Me) from 2a. To a stirred solution of **2a** (78.7 mg, 0.378 mmol) in MeOH (3 mL) was added concentrated H_2SO_4 (three drops) at room temperature. After being stirred for 6 h, the mixture was quenched with aqueous $NaHCO_3$ and then concentrated to ca. 1 mL of the total volume. The residue was taken up in ether and worked up to give **8a**[18] (52.1 mg, 100%) after chromatography. Similarly, **8a** was also obtained from **11** in 97% yield.

In a similar manner, **4-(ethoxymethyl)phenol (8b, R = Et)**[18] was obtained in 99% yield as well as in 85% yield from **11**.

4-Hydroxybenzyl Alcohol (11) from 2a. Hydrolysis of **2a** (54.0 mg, 0.260 mmol) with aqueous 2% $HClO_4$ (2 mL) in THF (1 mL) for 8 h at 50 °C gave **11**[19] (89%).

2-Bromo-4-(methoxymethyl)phenol (9a, R = Me, Y = H) from 8a. To a solution of **8a** (468 mg, 3.39 mmol) in CCl_4 (9 mL) and MeOH (2 mL) was added a solution of Br_2 (0.164 mL, 3.20 mmol) in CCl_4 (2 mL) at ca. 4 °C. The usual workup gave **9a** (78%), **9b** (R = Me, Y = Br, 8%), and **8a** (13%), after chromatography.

9a: mp 59–60 °C; IR (neat) 3240 (OH), 1611, 1585 cm^{-1}; NMR ($CDCl_3$) δ 3.36 (s, 3, CH_3), 4.36 (s, 2, CH_2), 6.06 (br s, 1, OH), 6.95 (d, 1, J = 7.8 Hz, ArH), 7.17 (dd, 1, J = 7.8, 1.5 Hz, ArH), 7.47 (d, 1, J = 1.5 Hz, ArH). Anal. Calcd for $C_8H_9BrO_2$: C, 44.27; H, 4.12. Found: C, 44.08; H, 4.21. Methanolysis of **12a** in the presence of concentrated H_2SO_4 also gave **9a** in 89% yield.

2,6-Dibromo-4-(methoxymethyl)phenol (9b): mp 67–68 °C; IR (Nujol) 3240 (OH), 1598, 1559 cm^{-1}; NMR ($CDCl_3$) δ 3.36 (s, 3, CH_3), 4.32 (s, 2, CH_2), 5.83 (br s, 1, OH), 7.42 (s, 2, ArH). Anal. Calcd for $C_8H_8Br_2O_2$: C, 32.47; H, 2.72. Found: C, 32.59; H, 2.46.

Similarly, **2-bromo-4-(ethoxymethyl)phenol (9c, R = Et, Y = H)** and **2,6-dibromo-4-(ethoxymethyl)phenol (9d, R = Et, Y = Br)** were obtained from **8b** in 80% and 7% yields.

9c: mp 70–71 °C; IR (Nujol) 3190 (OH), 1612, 1584, 1511 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 3, CH_3), 3.53 (q, 2, CH_2O), 4.41 (s, 2, CH_2), 5.78 (br s, 1, OH), 6.96 (d, 1, J = 7.8 Hz, ArH), 7.20 (dd, 1, J = 7.8, 1.5 Hz, ArH), 7.49 (d, 1, J = 1.5 Hz, ArH). Anal. Calcd for $C_9H_{11}BrO_2$: C, 46.78; H, 4.80. Found: C, 46.84; H, 4.66.

9d: mp 92–93.5 °C; IR (Nujol) 3190 (OH), 1600, 1558, 1482 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, 3, CH_3), 3.52 (q, 2, CH_2O), 4.37 (s, 2, CH_2), 6.93 (br s, 1, OH), 7.43 (s, 2, ArH). Anal. Calcd for $C_9H_{10}Br_2O_2$: C, 34.87; H, 3.25. Found: C, 35.06; H, 3.47.

3-Bromo-4-hydroxybenzyl Alcohol (12a, Y = H) from 11. To a stirred solution of **11** (248 mg, 2.0 mmol) and $CaCO_3$ (412 mg, 4.11 mmol) in EtOH (2 mL) under N_2 was added a solution of Br_2 (0.14 mL, 2.7 mmol) in EtOH (1.4 mL) for 5 h at ca. −4 °C. The usual workup gave **12a**[20] (87%) and **12b**[21] (Y = Br, 7%), after chromatography.

2-Bromo-6-methoxy-4-methylphenol (15) from 2,6-Dibromo-4-methylphenol (14). A solution of **14** (52.2 mg, 0.196 mmol) and BaO (468 mg, 3.052 mmol) in MeOH (3 mL) under N_2 was refluxed for 1.5 h at 90 °C and worked up in the usual manner to give **15**[22] (77%), **16**[23] (3%), and the recovered **14** (10.3 mg, 20%), after chromatography.

2,6-Dimethoxy-4-methylphenol (16) from 14. The treatment of **14** with BaO and $CuCl_2$ in MeOH–DMF under N_2 gave **16**

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(88%) along with **15** (10%), after chromatography.

Registry No. 1, 140-39-6; **2a**, 2937-64-6; **2b**, 71118-97-3; **3**, 7143-16-0; **4a**, 878-00-2; **4b**, 123-08-0; **5a**, 2973-78-6; **5b**, 2973-77-5; **6a**, 121-33-5; **6b**, 121-32-4; **6c**, 71118-98-4; **6d**, 71118-99-5; **7a**, 13287-30-4; **7b**, 71119-00-1; **8a**, 5355-17-9; **8b**, 57726-26-8; **9a**, 71119-01-2; **9b**, 71119-02-3; **9c**, 71119-03-4; **9d**, 71119-04-5; **10a**, 5533-03-9; **10b** (R' = Et), 5595-79-9; **10b** (R' = *i*-Pr), 71119-05-6; **10b** (R' = Bu), 71119-06-7; **10c**, 71119-07-8; **11**, 623-05-2; **12a**, 29922-56-3; **14**, 2432-14-6; **15**, 71119-08-9; **16**, 6638-05-7; a, 104-93-8; b, 104-21-2; c, 14202-31-4; d, 63866-99-9; e, 71155-68-5; 2-bromophenol, 95-56-7; 4-bromophenol, 106-41-2; methanol, 67-56-1; ethanol, 64-17-5; 2-propanol, 67-63-0; butanol, 71-36-3; 2-methoxyphenol, 90-05-1; 4-methoxyphenol, 150-76-5.

Ion Radicals. 44. Reactions with 10-Phenylphenoxazine Cation Radical Perchlorate[1,2]

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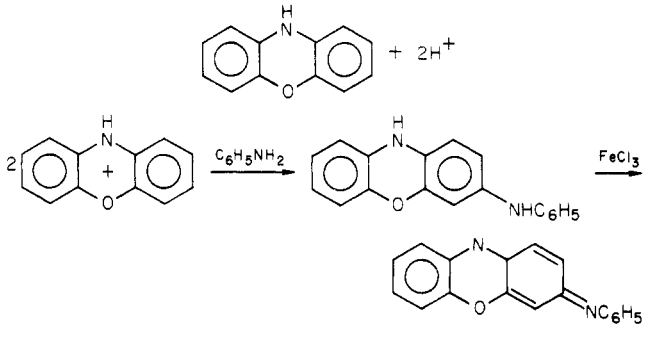
10-Phenylphenoxazine cation radical perchlorate ($1^{+}\cdot,ClO_4^-$) was prepared by oxidation of **1** with $I_2/AgClO_4$. Reaction of $1^{+}\cdot$ with NO_2^-, SCN^-, and Br^- gave excellent yields of 3-nitro- (**2**), 3-thiocyano- (**3**), and 3-bromo-10-phenylphenoxazine (**4**). Reaction with Cl^- gave only 14% of 3-chloro-10-phenylphenoxazine (**6**). Reaction with Br^- gave also 1.9% of 3,7-dibromo-10-phenylphenoxazine (**5**), while reaction with Cl^- gave also 10% of 7,7'-dichloro-3,3'-bis(10-phenylphenoxazine) (**7**) and 74% of **1**. Reaction with H_2O and CH_3OH gave only **1** and 3,3'-bis(10-phenylphenoxazine) (**8**), the latter being in yields of about 45%. Reaction with CN^-, $O_2^{-}\cdot$, diethylamine, diisopropylamine, and butylamine gave mostly **1** (78–92%) and smaller amounts of **8**. Reaction with F^- gave mostly **1** with a small amount of **8** and monofluoro **8** (**9**). Authentic **2** was prepared, and from it authentic **4** and **6** were obtained. During the preparation of **2**, some peculiarities in the melting point of 3-nitrophenoxazine were observed but not resolved.

Oxidized states of phenoxazines are to be found in important dyestuffs and indicators (Meldola's blue, litmus) and in some naturally occurring antibiotics (actinomycins) and pigments.[3] Yet, little is known of the chemistry of the primary, one-electron oxidation states (the cation radicals) of phenoxazines. This is in contrast with what is known about the cation radicals of the analogous thianthrene, phenoxathiin, and phenothiazine.[4,5] The phenoxazine cation radical itself has, nevertheless, been known for many years, having been made by Kehrmann in the early 1900s by the oxidation of phenoxazine with Br_2 and $FeCl_3$.[6] The radical nature of the oxidation product was not, of course, recognized, although Kehrmann understood clearly that two stages of oxidation could occur and classified the products later, from oxidations with H_2O_2 in H_2SO_4 and H_2O_2 in $HClO_4$–acetic acid, as mono- and diacid salts. The monoacid salt solution had λ_{max} at 530 nm and the diacid salt solution at 460 nm,[7] which we would now attribute, respectively, to the mono- and dication resulting from one- and two-electron oxidation. The correct formulation of the cation radical was made by Weitz and Schwechten in 1926[8] and was confirmed experimentally later by others with the potentiometric titration of phenoxazine with $Pb(OAc)_4$ in acetic acid[9] and photoionization at low temperature.[10] Confirmation of the cation radical's structure by ESR spectroscopy followed, with low-resolution spectra in 1962[11] and complete-resolution spectra in later years.[12-14]

Scheme I



The only other phenoxazine cation radicals which have received attention are the 10-aryl ones. Detailed ESR characterization of a series of these has been made, in which the cation radicals were obtained by oxidation with nitromethane solutions of $AlCl_3$, $Tl(OAc)_3$, or H_2SO_4.[15] The 10-phenylphenoxazine cation radical has also been obtained by oxidation of the parent compound with $FeCl_3$ in acetic acid.[16]

Among these studies, however, no deliberate attempts have been made to study the chemistry of the cation radicals. Musso found that in neutral and alkaline solutions phenoxazine cation radical gave the 1,10' and 3,10' dimers of phenoxazine,[16,17] while Tsujino found that these

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