The Characterization of Complex Phenols by Nuclear Magnetic Resonance Spectra

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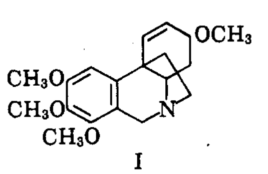
The characterization of complex phenols may be aided by comparing the n.m.r. spectrum of the phenol with that of its anion. The chemical shifts of the aromatic protons of the anion in deuterium oxide solution occur at higher field than those of the phenol in deuteriochloroform by characteristic amounts. Phenols bearing only alkyl or alkoxyl substituents show the following upfield changes: *ortho,* 0.16–0.28 p.p.m.; *meta,* 0.05–0.11 p.p.m.; *para,* 0.32–0.39 p.p.m. Comparison in dimethyl sulfoxide solution leads to these ranges: *ortho,* 0.42–0.59; *meta,* 0.19–0.38; *para,* 0.71–0.79 p.p.m. Phenols bearing other substituents may be characterized by study of appropriate models. Conversion to the acetate produces less explicit downfield changes.

In the course of structural determination of naturally occurring or synthetic compounds there occasionally arises the problem of locating a phenolic hydroxyl group on a polysubstituted aromatic ring. An example is the phenolic alkaloid amaryllisine whose investigation demonstrated that the monomethyl ether of the alkaloid is represented by I.[1] To determine which oxygenated position of the aromatic ring of the parent alkaloid bears the free phenolic group, a method was sought which would avoid tedious chemical degradation and allow the study of materials available only in small quantity. The difference in chemical shift between the aromatic protons of the phenol and its anion has been found to provide the basis for such a method.



I

The chemical shifts of the aromatic protons of nine phenols and the corresponding anions are tabulated in Table I. It is clear that, on conversion to the anion, the resonance of the aromatic protons is shifted generally upfield, but the increment is characteristic of the position of the proton relative to the phenolic group. Thus, the *para* proton is shifted by about 0.35 p.p.m. and the *ortho* by about 0.2 p.p.m., while the *meta* is very little affected. As the ranges do not overlap, the comparison of the spectrum of an unknown phenol bearing methyl or methoxyl groups with that of its anion unambiguously reveals the position of the aromatic protons in relation to the phenolic group.

In hope that similar studies might provide substantiating evidence in such problems, the spectra of various derivatives were examined. The spectral data for acetates and picryl ethers are tabulated as Table II. Both show general downfield shifts. The proton resonance changes in acetate formation are centered at -0.17, -0.08, and -0.30 p.p.m. for *ortho, meta,* and *para* protons, respectively, but, as the ranges overlap, a change observed for an unknown phenol may not be explicit. Converting a phenol to the corresponding picryl ether shifts the *para* proton an amount similar to that of acetate formation, but the *ortho* and *meta* protons fail to show any consistent behavior. Preliminary studies showed that converting a phenol to its methyl ether produced very little change in the chemical shifts, while the tosylate spectra resemble those of the acetate, with the inconvenient addition of two groups of peaks in the aromatic region.

To learn whether the ranges established above apply to phenols bearing more widely varying substituents, six additional phenols, their anions, and their acetates were examined. The data of Tables Ib and IIb show that the resonance changes observed fall outside the previous ranges. The possibility of studying such phenols by these means is further examined below.

The question whether a rational origin of these changes might be found led to the examination of the spectra of 22 phenols and their sodium salts in dimethyl sulfoxide solution, which allows the comparison of spectra without the complication of a change in solvent. As can be seen in the data of Table III, the changes observed were larger and occurred in somewhat narrower ranges. Thus, conversion of simply substituted phenols to their sodium salts shifts the *ortho* proton 0.50–0.59 p.p.m. upfield (with the single exception of 2-methoxyl-5-methylphenol, 0.42 p.p.m.); the *meta* proton was moved upfield 0.19–0.38 p.p.m., and the *para* 0.71–0.79 p.p.m. Again, the examination of more variously substituted phenols showed that the changes for these compounds were not confined to these ranges. However, the eight phenols examined which bear the phenolic group *para* to a carbonyl system or vinylogous carbonyl system show changes within the limits, *ortho* 0.60–0.84 and *meta* 0.22–0.47 p.p.m. Thus, in an unknown *p*-ketophenol, comparison of the phenol and anion spectra will allow the protons to be distinguished. One may confidently anticipate that other series represented by the remaining compounds of Table III may be studied by such spectral changes by extension to a suitable group of model compounds.

Thus, the study of the effect of anion formation in polysubstituted phenols can reveal the position of remaining protons. The data here suffice for the study of phenols substituted by alkoxyl or alkyl groups. When the properties of the unknown phenol allow ready recovery from dimethyl sulfoxide, or when recovery is not necessary, the more discrete ranges observed for this solvent recommend its use. However, the more facile recovery possible from deuteriochloroform and deuterium oxide may occasionally prescribe their employment.

Origin of the Spectral Changes.—It is now well established that the chemical shifts of protons on aromatic rings reflect the charge density on the carbon

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[1] A. L. Burlingame, H. M. Fales, and R. J. Highet, *J. Am. Chem. Soc.*, **86**, 4976 (1964).

TABLE I

CHEMICAL SHIFTS OF PHENOLS AND ANIONS[a]

Phenol	Phenol[b]			Phenol anion[c]			Change		
	o	m	p	o	m	p	o	m	p
	A. Methyl- and Methoxyl-Substituted Phenols								
p-Methoxyphenol	3.23	3.23		3.44	3.22		0.21	−0.01	
2,6-Dimethoxyphenol		3.41	3.20		3.37	3.60		−0.04	0.40
p-Cresol	3.26	2.97		3.47	3.08		0.21	0.11	
2,6-Dimethylphenol		3.02	3.24		3.08	3.62		0.06	0.38
3,5-Dimethylphenol	3.53		3.43	3.75		3.75	0.22		0.32
2,4-Dimethylphenol	3.33	3.05 3.12 [d]		3.52	3.11 3.22 [d]		0.19	0.06 0.10 [d]	
2,5-Dimethylphenol	3.42	3.00	3.33	3.58	3.08	3.70	0.16	0.08	0.37
2-Methoxy-4-methylphenol	3.17	3.32 3.34 [d]		3.45	3.30 3.45 [d]		0.28	−0.02 0.11 [d]	
2-Methoxy-5-methylphenol	3.32	3.25	3.38	3.57	3.27	3.73	0.25	0.02	0.35
						Range:	0.16–0.28	−0.04–0.11	0.32–0.40
	B. Other Phenols								
Methyl syringate		2.67			2.83			0.16	
Vanillin	2.93	2.55		3.49	2.95 2.80 [d]		0.56	0.40 0.25 [d]	
Isovanillin	2.56	3.04	2.57	3.00	3.13	2.99	0.44	0.09	0.42
p-Nitrophenol	3.07	1.80		3.60	2.10		0.53	0.30	
p-Chlorophenol	3.22	2.80		3.43	3.01		0.21	0.21	
p-Hydroxybenzaldehyde	3.00	2.15		3.42	2.36		0.42	0.21	

[a] Data given are in the τ-scale. [b] In deuteriochloroform solution. [c] In deuterium oxide solution. [d] The upper value of the pair is that of the 3-proton and lower that of the 5-proton.

TABLE II

CHEMICAL SHIFTS OF PHENOL ACETATES AND PICRYL ETHERS

Phenol	Phenol acetate						Picryl ether					
	Chemical shifts[a]			Change			Chemical shifts[a]			Change		
	o	m	p	o	m	p	o	m	p	o	m	p
	A. Methyl- and Methoxyl-Substituted Phenols											
p-Methoxyphenol	2.98	3.08		−0.25	−0.15		3.13	3.13		−0.10	−0.10	
2,6-Dimethoxyphenol		3.37	2.87		−0.04	−0.33		3.38	2.88		−0.03	−0.32
p-Cresol	3.02	2.83		−0.24	−0.14		3.20	2.85		−0.06	−0.12	
2,6-Dimethylphenol		2.97	2.97		−0.05	−0.27		2.92	2.92		−0.10	−0.32
3,5-Dimethylphenol	3.28		3.13	−0.25		−0.30	3.50		3.18	−0.03		−0.25
2,4-Dimethylphenol	3.10	2.97 3.00 [b]		−0.23	−0.08 −0.12 [b]		3.63	2.90 3.15 [b]		0.30	−0.15 0.03 [b]	
2,5-Dimethylphenol	3.15	2.88	3.05	−0.27	−0.12	−0.28	3.72	2.83	3.09	0.30	−0.17	−0.24
2-Methoxy-4-methylphenol	3.07	3.17 3.32 [b]		−0.10	−0.15 −0.02 [b]							
2-Methoxy-5-methylphenol	3.12	3.14	3.02	−0.20	−0.11	−0.36						
			Range:	−0.10–−0.27	−0.02–−0.15	−0.27–−0.36						
	B. Other Phenols											
Methyl syringate		2.63			−0.04							
Vanillin	2.76	2.47 2.49 [b]		−0.17	−0.08 −0.06 [b]							
Isovanillin	2.41	2.93	2.23	−0.15	−0.11	−0.34						
p-Nitrophenol	2.83	1.87		−0.24	0.07							
p-Chlorophenol	2.95	2.67		−0.27	−0.13							
p-Hydroxybenzaldehyde	2.71	2.07		−0.29	−0.08							

[a] In deuteriochloroform solution; data given are in the τ-scale. [b] The upper value is that of the 3-proton and the lower that of the 5-proton.

atom to which the protons are attached,[2] and evidence has been presented that the relation between chemical shift and charge density is governed by the expression

$$\Delta\tau = k(\Delta q)$$

in which $\Delta\tau$ represents the difference in the chemical shift from that of benzene, an upfield shift being taken as positive, and Δq represents the excess in the charge density from unity (which is the density on benzene carbon atoms).[3] The constant k has been estimated at 10.7 p.p.m./electron from the observation that, for the cyclopentadienyl anion ($\Delta q = 1/5$), $\Delta\tau = 1.72$ and, for the tropylium cation ($\Delta q = -1/7$), $\Delta\tau = -1.9$.[3] The relation is clearly consistent with the qualitative

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(2) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 256–264.

(3) (a) G. Fraenkel, R. E. Carter, A. M. McLachlean, and J. H. Richards, *J. Am. Chem. Soc.*, **82**, 5846 (1960); (b) H. Spiesecke and W. G. Schneider, *Tetrahedron Letters*, 468 (1961); (c) P. C. Lauterbur, *ibid.*, 247 (1961).

TABLE III

CHEMICAL SHIFTS OF PHENOLS AND ANIONS IN DIMETHYL SULFOXIDE[a]

Phenol	OH	Phenol			Anion			Change		
		o	*m*	*p*	*o*	*m*	*p*	*o*	*m*	*p*
Methyl- and Methoxyl-Substituted Phenols										
p-Methoxyphenol	1.15	3.25	3.25		3.84	3.55		0.59	0.30	
2,6-Dimethoxyphenol	1.80		3.37	3.27		3.57	3.98		0.20	0.71
p-Cresol	0.82	3.28	3.00		3.85	3.38		0.57	0.38	
3,5-Dimethylphenol	0.97	3.59		3.59	4.10		4.32	0.51		0.73
2,4-Dimethylphenol	1.13	3.37	3.13[b] 3.20		3.92	3.42[b] 3.55		0.55	0.29[b] 0.35	
2,5-Dimethylphenol	0.98	3.39	3.07	3.48	3.92	3.37	4.23	0.53	0.30	0.75
2-Methoxy-4-methylphenol	1.45	3.28	3.27[b] 3.45		3.78	3.60[b] 3.63		0.50	0.33[b] 0.18	
2-Methoxy-5-methylphenol	1.30	3.38	3.20	3.47	3.80	3.56	4.20	0.42	0.36	0.73
2,6-Dimethylphenol	1.91		3.08	3.35		3.37	4.14		0.29	0.79
3,5-Dimethoxyphenol	0.63	4.02		4.02	4.52		4.75	0.50		0.73
							Range:	0.42–0.59	0.19–0.38	0.71–0.79
Phenols Bearing a *p*-Acyl Group or Vinylogous Acyl Group										
Methyl syringate	~0.80		2.73			2.95			0.22	
Vanillin	...	2.98	2.57[b] 2.53		3.73	3.00[b] 2.85		0.75	0.43[b] 0.32	
p-Hydroxybenzaldehyde	−0.58	3.00	2.17		3.80	2.63		0.80	0.46	
p-Hydroxyacetophenone	−0.33	3.10	2.13		3.86	2.48		0.76	0.35	
4-Hydroxy-2-methylacetophenone	−0.10	3.28[c] 3.27	2.20		4.05[c] 4.03	2.55		0.77[c] 0.76	0.35	
4-Hydroxy-3-methylacetophenone	−0.23	3.10	2.23[c] 2.30		3.94	2.53[c] 2.60		0.84	0.30[c] 0.30	
Vanillalacetone	~0.50	3.15	2.65[b] 2.82		3.75	3.12[b] 3.07		0.60	0.47[b] 0.25	
7-Hydroxy-4-methylcoumarin	~0.00	3.14[d] 3.25	2.39		3.80[d] 4.05	2.83		0.66[d] 0.80	0.44	
							Range:	0.60–0.84	0.22–0.47	
Other Phenols										
Isovanillin	0.45	2.69	2.87	2.57	3.22	3.23	3.33	0.53	0.36	0.76
p-Nitrophenol	...	3.00	1.82		3.92	2.18		0.92	0.36	
p-Chlorophenol	0.35	3.20	2.79		3.84	3.28		0.64	0.49	
2,5-Dichlorophenol	−0.65	2.97	2.62	3.13	3.64	3.05	4.07	0.67	0.43	0.94
2-Hydroxy-4-methoxyacetophenone	−2.70	3.50	2.14	3.47	4.15	2.60	4.38	0.65	0.46	0.91

[a] Data given are in the τ-scale. [b] The upper value is for the 3-proton, the lower for the 5-proton. [c] The upper value is for the 2-proton, the lower for the 6-proton. [d] The upper value is for the 6-proton, the lower for the 8-proton.

TABLE IV

COMPARISON OF CALCULATED CHARGE DENSITIES WITH CHEMICAL SHIFTS

Proton position	Calculated charge densities					Chemical shift change, p.p.m.
	LCAO,[a] phenol	SCF,[b] phenol	SCF,[c] phenolate	Difference (SCF)	LCAO,[d] HFMO[e]	
ortho	1.040	1.008	1.027	0.019	0.244	0.42–0.59
meta	0.999	1.012	1.042	0.030	0.098	0.19–0.38
para	1.029	1.000	1.130	0.130	0.564	0.71–0.79

[a] Ref. 6. [b] Ref. 7. [c] Ref. 8. [d] Ref. 10. [e] Charge density in the highest filled molecular orbital, calculated by standard LCAO methods.

generalization that an increase in electron density, by increasing the shielding of a proton, produces an upfield change in the chemical shift of the proton. Recently, Schaefer and Schneider have presented an extensive investigation of the success of this relation in correlating the chemical shifts of various aromatic compounds and the local charge distributions predicted by various molecular orbital calculations.[4] Although some striking discrepancies appear in polycyclic and heterocyclic systems, this investigation showed a generally satisfying correlation.

The observations on substituted benzenes are closely parallel: electron-withdrawing substituents produce downfield shifts in the *ortho* and *para* protons, while electron-donating substituents produce an upfield shift. It is quite generally observed that the *ortho* protons are more affected than the *para*.[5] Zweig, Lehnsen, Lancaster, and Neglia have shown that a plot of the chemical shifts of the aromatic protons of various methoxybenzenes against the charge density calculated by a simple LCAO method clusters closely about a line of slope 10 p.p.m./electron.[6] These

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(4) T. Schaefer and W. G. Schneider, *Can. J. Chem.*, **41**, 966 (1963).

(5) (a) P. L. Corio and B. P. Daily, *J. Am. Chem. Soc.*, **78**, 3043 (1956); (b) A. A. Bothner-By and R. E. Glick, *J. Chem. Phys.*, **26**, 1951 (1957); (c) J. N. Shoolery, *ibid.*, **21**, 1899 (1953); (d) H. Spiesecke and W. G. Schneider, *ibid.*, **35**, 731 (1961).

(6) A. Zweig, J. E. Lehnsen, J. E. Lancaster, and M. T. Neglia, *J. Am. Chem. Soc.*, **85**, 3940 (1963).

TABLE V

	B.p. (mm.) or m.p., °C.			Acetate			Picryl ether						
				B.p. (mm.) or m.p., °C.				Calcd., %			Found, %		
Compound	Obsd.	Lit.	Ref.	Obsd.	Lit.	Ref.	M.p., °C.	C	H	N	C	H	N
p-Methoxyphenol	53–54	53	*a*	33–34	31–32	*b*	149.5–151	46.37	3.09	12.34	46.57	2.71	12.54
2,6-Dimethoxyphenol	56–57	54.8	*c*	53.5–55.5	53.5	*c*	152.5–155	46.03	3.04	11.51	45.77	3.13	11.42
Cresol	30–33	36	*d*	n^{28}_{D} 1.4969	n^{23}_{D} 1.4991	*e*	102–103.5	48.91	2.84	13.16	49.02	2.96	13.33
3,5-Dimethylphenol	63.5–64	64	*f*	116–119 (7)	120 (15)	*g*	196–197	50.45	3.33	12.61	50.18	3.44	12.67
		68	*h*		118–120 (19)	*i*							
2,4-Dimethylphenol	19–21	25.4–26	*j*	96–103 (11)	107.5–108 (13)	*k*	114–116	50.45	3.33	12.61	50.78	3.67	12.33
				n^{28}_{D} 1.4956	n_{D} 1.4990								
2,5-Dimethylphenol	77–78	74.5	*l*	d^{25}_{20} 1.021	*d* 1.0264	*l*	166.5–168	50.45	3.33	12.61	50.29	3.45	
2-Methoxy-4-methylphenol	108–109 (18)	113.5 (22)	*m*	253–255 (755)	246–248	*n*	189–191.5	48.14	3.17	12.03	48.18	3.43	11.97
	n^{28}_{D} 1.5327	n_{D} 1.5353											
2-Methoxy-5-methylphenol	32.5–36	37–39	*o*	56–57	56–57	*p*							
2,6-Dimethylphenol	45–46	47–48	*q*	218.7–220 (755)	214–216	*r*							
Methyl syringate	106–107	107	*s*	133–134	129	*t*							
Vanillin	82–83	80–81	*u*	80.5–81.5	77	*v*							
Isovanillin	115–116	116–117	*w*	86–88	88	*x*							
p-Nitrophenol	117–119	114	*y*	80.5–81.5	81–82	*z*							
p-Chlorophenol	35–39	41	*aa*	226–229 (750)	226–228	*aa*							
p-Hydroxybenzaldehyde	114.5–121.5	115–116	*bb*	150–152 (15)	152–153 (17)	*cc*							
p-Hydroxyacetophenone	103–106	107	*dd*										
4-Hydroxy-2-methylacetophenone	128.5–132	126	*ee*										
4-Hydroxy-3-methylacetophenone	107–111	104	*ff*										
Vanillalacetone	127.5–129	130	*gg*										
7-Hydroxy-4-methylcoumarin	186.5–189	185–186	*hh*										
2,5-Dichlorophenol	55–57	58	*ii*										
2-Hydroxy-4-methoxyacetophenone	48.5–51	50	*jj*										

[a] H. Hlasiwetz and J. Haberman, *Ann.*, **177**, 340 (1875). [b] A. Klemenc, *Monatsh.*, **35**, 90 (1914). [c] C. Graebe and H. Hess, *Ann.*, **340**, 234 (1905). [d] L. Barth, *ibid.*, **154**, 358 (1870). [e] J. H. Gladstone, *J. Chem. Soc.*, 246 (1884). [f] A. Thol., *Ber.*, **18**, 362 (1885). [g] K. v. Auwers and E. Borshe, *ibid.*, **48**, 1708 (1915). [h] E. Nolting and S. Forel, *ibid.*, **18**, 2679 (1885). [i] L. I. Smith and J. W. Opie, *J. Org. Chem.*, **6**, 429 (1941). [j] O. Jacobsen, *Ber.*, **18**, 3464 (1885). [k] L. Palfray and T. Duboc, *Compt. rend.*, **185**, 1480 (1927). [l] O. Jacobsen, *Ber.*, **11**, 27 (1878). [m] M. O. De Vries, *Rec. trav. chim.*, **28**, 282 (1909). [n] F. Tiemann, *Ber.*, **9**, 418 (1876); F. Tiemann and B. Mendelsohn, *ibid.*, **10**, 58 (1877). [o] W. H. Perkin, *J. Chem. Soc.*, 1185 (1896). [p] F. R. Graesser-Thomas, J. M. Gulland, and R. Robinson, *ibid.*, 1973 (1926). [q] O. Jacobsen, *Ber.*, **21**, 2829 (1888). [r] K. v. Auwers and W. Mauss, *Ann.*, **460**, 266 (1928). [s] C. Graebe and E. Martz, *Ber.*, **36**, 217 (1904). [t] M. T. Bogert and E. Plant, *J. Am. Chem. Soc.*, **37**, 2729 (1915). [u] P. Carles, *Bull. soc. chim. France*, [2] **17**, 18 (1872). [v] F. Tiemann and N. Nagai, *Ber.*, **11**, 647 (1878). [w] R. Wegscheider, *Monatsh.*, **3**, 792 (1882). [x] E. Pascu and L. v. Vargha, *Ber.*, **59**, 2821 (1926). [y] P. Wagner, *ibid.*, **7**, 77 (1874); R. Fittig, *ibid.*, **7**, 280 (1874); R. Schiff, *Ann.*, **223**, 263 (1884). [z] E. Noelting, E. Grandmougin, and O. Michel, *Ber.*, **25**, 3336 (1892). [aa] Dubois, *Z. Chem.*, 205 (1867); W. Wohlleben, *Ber.*, **42**, 4372 (1909). [bb] K. Reimer and F. Tiemann, *Ber.*, **9**, 824 (1876). [cc] H. Staudinger and N. Kon, *ibid.*, **38**, 92 (1911). [dd] J. Klingel, *ibid.*, **18**, 2691 (1885). [ee] M. Nencki and E. Stoeber, *ibid.*, **30**, 1770 (1897). [ff] J. Klingel, *ibid.*, **18**, 2699 (1885). [gg] F. Tiemann, *ibid.*, **18**, 3492 (1895). [hh] H. v. Pechmann, *Ann.*, **261**, 169 (1891). [ii] E. Noelting and E. Kopp, *Ber.*, **38**, 3510 (1905). [jj] Y. Tahara, *ibid.*, **24**, 2460 (1888).

results are applicable to the phenols treated in this paper, for the chemical shift of the phenol is little affected by etherification, and parameters for the HMO calculations are the same. Choosing parameters for the phenol anion is quite difficult. However, SCF calculations for the neutral phenol[7] and the anion have been published,[8] and the charge densities are compared in Table IV. As anticipated from the change in chemical shift, the *para* charge difference is greater than the *ortho*. However, the calculated charge differences for both *meta* and *para* protons are much too large. Furthermore, the charge densities calculated by the SCF method for the neutral phenol are substantially different from the LCAO calculation, which corresponds much better to the chemical shifts. The charge density figures for both the phenol and the anion are anomalous in showing a much higher density at the *meta* position than anticipated from simple resonance theory, or from the reactions of phenol and its ion. It would appear that the SCF approach must be further modified to provide adequate charge densities.

Other workers have correlated the charge density of the highest filled orbital of aromatic systems with phenomena qualitatively connected with electron density, such as reactions with electrophilic agents.[9] This quantity is tabulated in Table IV, as derived from simple LCAO calculations for phenol.[10] It can be seen that the order of these values is that of the chemical shift changes, and that there is a roughly linear relation. The earlier use of this quantity was based on an intuitive concept of intermediate states in chemical reactions which is not applicable to the present problem, and, although it is not unreasonable that the difference in charge distribution between phenol and its anion may be related to the charge distribution of the highest filled molecular orbital, no deductive relation can be stated at this time. A more satisfactory interpretation of the phenomena described here must await further studies.

Experimental

The phenols used were obtained from commercial sources and crystallized or distilled as required to give materials whose properties are presented in Table V. Phenol acetates were obtained by refluxing the phenol in excess acetic anhydride for 30 min., destroying the excess anhydride with 1 *N* potassium bicarbonate solution, and extracting the phenol acetate with ether. The ethereal extracts were washed with dilute sodium hydroxide, the ether was removed by distillation, and the residue was crystallized or distilled under reduced pressure to provide materials whose physical properties are presented in Table V. Infrared spectra of these materials were consistent with the structure assigned.

Isovanillin acetate prepared by this procedure was grossly contaminated with the triacetate. The material described in Table V was prepared by treating the phenol with acetic anhydride in pyridine solution.

The phenol picryl ethers were prepared by stirring a benzene solution of picryl chloride with an aqueous solution of the sodium salt of the phenol in equimolar amounts. After 16 hr. the benzene layer was washed with dilute sodium hydroxide and distilled to dryness under reduced pressure, and the residue was crystallized from an ethyl acetate–benzene mixture to provide the materials described in Table V.

N.m.r. spectra of the compounds were determined on a Varian A-60 n.m.r. spectrometer. Phenolate solutions in deuterium oxide were prepared by dissolution of *ca.* 0.15 mmole of phenol in 0.3 ml. of 0.5 *N* sodium deuterioxide solution, prepared by the cautious addition of sodium metal to deuterium oxide. Peak positions were determined relative to external cyclohexane, which was assigned a value of τ 8.88 for this study. (An external sample of cyclohexane in deuteriochloroform shows a peak 67 c.p.s. below internal tetramethylsilane, τ 10.00.) Other spectral data of Tables I and II were measured in deuteriochloroform solution relative to internal tetramethylsilane, τ 10.0. The phenolate salts of Table III were prepared by treating the phenol with an equivalent amount of 2.5 *N* sodium hydroxide, and distilling the sample to dryness under reduced pressure. Measurements were made in dimethyl sulfoxide solution, of approximately 9% w./v., relative to internal tetramethylsilane, τ 10.0. The use of deuterated dimethyl sulfoxide was not necessary, as the solvent peaks appeared between 70 and 220 c.p.s. and did not obscure the peaks studied.

Interpretation of the N.m.r. Spectra.—2,6-Disubstituted phenols give rise to AB_2 spectra readily interpretable with the aid of standard reference works.[11] Of the nine lines of the spectrum, the third occurs at the chemical shift of the single proton H_A, while the average of the fifth and the seventh is that of H_B. Comparison with sample computed spectra makes it easy to choose which end of the spectrum to start numbering from, *i.e.*, whether $\tau_A > \tau_B$, or *vice versa*.

3,5-Disubstituted phenols give rise to spectra with two broad peaks, the larger centered at the chemical shift of the 2- and 6-protons, and the smaller centered at that of the 4-proton.

para-Substituted phenols constitute an A_2B_2 system which gives rise to a complex spectrum; however, for purposes of determining the chemical shifts in the systems in hand, it is sufficient to treat the pattern as the quartet of an AB system.[12] As these spectra provide no internal evidence for distinguishing between the 2,6-protons and the 3,5-protons, the shifts were assigned to be consistent with known substituent effects,[2,5] and other observations described herein. The results from *p*-methoxybenzene and *p*-cresol do not constitute independent evidence for the shifts adduced, but do show the requisite consistency.

A spectrum of a 2,4- or 2,5-disubstituted phenol comprises three groups: a doublet separated by approximately 2 c.p.s. from *meta* coupling, a doublet separated by approximately 9 c.p.s. from *ortho* coupling, and a quartet split by both couplings. These three groups are commonly readily recognizable and allow unambiguous assignment of the chemical shifts. Near coincidence of the chemical shifts of protons *ortho* to each other produces a "deceptively simple spectrum" of a type commented on in flavonoid spectra. The larger peak is centered over the chemical shifts of the *ortho* protons, and the smaller over the remaining proton.[13]

The peaks of the other groups in the molecules appeared at shifts consistent with their nature and showed trivial changes on derivative formation or solvent change.

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