New Structures from Enzymic Dehydrogenation of Lignin Model *p*-Hydroxypropiophenones

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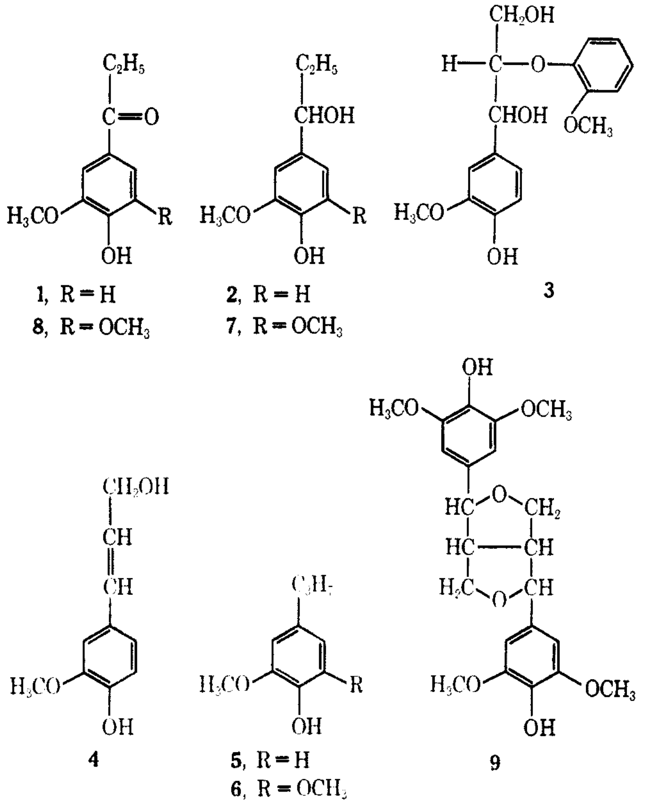
Enzymic dehydrogenation studies on lignin model *p*-hydroxypropiophenones have led to new concepts on some structural aspects of the lignin macromolecule. The main conclusions from these experiments are the prominence of *p*-cyclohexadienone radical participation during radical lignification reactions and the subsequent formation of *o,p'*-biphenyl linkages and of side chain transfer reactions leading to the formation of aryl esters of aliphatic acids, and, with some compounds, the free carboxylic acids themselves.

That lignin is a product of the coupling of phenoxy radicals formed by enzymic dehydrogenation of *p*-hydroxycinnamyl alcohols is now a widely accepted concept. Benzyl alcohol, benzyl ether, and carbonyl groups on α-C of the side chain are important structural features of the lignin molecules, and reviews of the means of detection and estimation of the amounts of each with both free and etherified *p*-phenolic hydroxyls have been published.[2] It has been found that these groups also play an important part in determining the nature of the products formed on dehydrogenation of various lignin model phenols.[3,4] The major models studied were propioguaiacone (**1**), α-ethylvanillyl alcohol (**2**), and guaiacylglycerol β-guaiacyl ether (**3**), and a preliminary report on the dehydrogenation of **1** and **2** has been published.[5] This article will deal only with *p*-hydroxypropiophenones. Full details of experiments on compounds with *p*-hydroxybenzyl alcohol and ether functions will be reported later.

In laboratory studies of the dehydrogenation of coniferyl alcohol (**4**), more than 40 low molecular weight lignin intermediates called lignols have been isolated and identified. Many of these are *p*-hydroxybenzyl alcohol and *p*-hydroxybenzyl ether compounds formed by respective addition of water and phenols onto intermediate quinone methides.[4]

We have found that on dehydrogenation of 4-propylguaiacol (**5**), the main products formed were straightforward dehydro dimers, the *o,o'*-dihydroxybiphenyl and the *o*-diphenyl ether; however, substantial amounts of similar compounds with α-carbinol groupings as well as α-ethylvanillyl alcohol (**2**) were also formed simultaneously through a quinone methide intermediate. 4-Propylsyringol (**6**) on dehydrogenation gave a nearly quantitative yield of α-ethylsyringyl alcohol (**7**) which on further dehydrogenation gives high yields of propiosyringone (**8**), while with syringaresinol (**9**) side chain oxidation also occurs (Chart I).[3]

CHART I



1, R = H
8, R = OCH_3
2, R = H
7, R = OCH_3
3
4
5, R = H
6, R = OCH_3
9

When **1** was dehydrogenated in aqueous solution with peroxidase and hydrogen peroxide in an amount calculated to remove 1 atom of hydrogen per molecule, the major compound formed (60% on basis of starting material) was the *o,o'*-dihydroxybiphenyl compound dehydrodipropioguaiacone (**10**). In addition, a resin which amounted to 24% of the starting compound was also formed. The major component of the resin (62%) has been identified as **11**, a terphenyl derivative having a novel *o,p'*-biphenyl bond and a phenolic propionate ester (Chart II).

Other compounds isolated and identified in the resin were the dimeric ester **12**, which comprised 6% of the resin, and which on saponification gives **13**, the *o*-diphenyl ether **14** which comprised 6% of the resin, and 10% each of the starting compound **1**, and the *o,o'*-dihydroxybiphenyl **10**. Also isolated in trace amounts was trimer **15**, a compound containing both the *o,o'*-biphenyl and the *o*-diphenyl ether bond. Nmr data for compounds **11**–**15** are given in Table I.

On reduction with $NaBH_4$ **14** and **15** gave compounds with uv spectra identical with those of compounds

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[1] Maintained at Madison, Wis., in cooperation with the University of Wisconsin.

[2] (a) E. Adler, *Paperi Puu*, **11**, 634 (1961); (b) E. Adler, H. D. Becker, T. Ishihara, and A. Stamvik, *Holzforschung*, **20**, 3 (1966).

[3] J. C. Pew, W. J. Connors, and A. Kunishi, *Chim. Biochem. Lignine, Cellulose, Hemicellulose, Actes Symp. Intern., Grenoble, France*, 1964, 229 (1965).

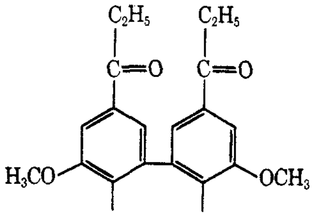
[4] K. Freudenberg, Advances in Chemistry Series, No. 59, American Chemical Society, Washington, D. C., 1966, pp 1–21.

[5] J. C. Pew and W. J. Connors, *Nature*, **215**, 623 (1967).

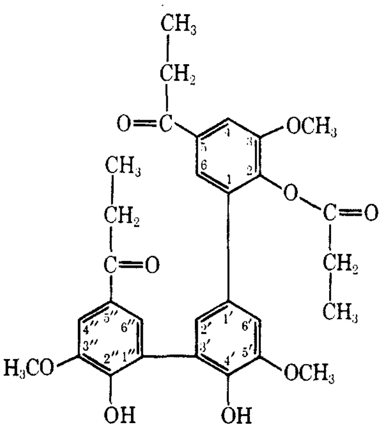
with saturated side chains previously synthesized in connection with work on 4-propylguaiacol.[3]

The propionate portion of **11** has been identified after saponification as free propionic acid by glpc,[6] and also as the 5-methoxytryptamine salt.[7] It is interesting to note that when this dehydrogenation was carried out in aqueous alcohol using 1 equiv of hydrogen peroxide, the propionate content of the total dehydrogenation product corresponded to a 49% yield of **11** on the basis of starting material, but this dehydrogenation resin appeared to be a more complex mixture than that from aqueous dehydrogenations and was not used for subsequent separations. The limited yield of **11** in aqueous solution is probably due to the insolubility of the intermediate biphenyl **10** which crystallizes out of the reaction mixture and is thus unavailable for further dehydrogenation.

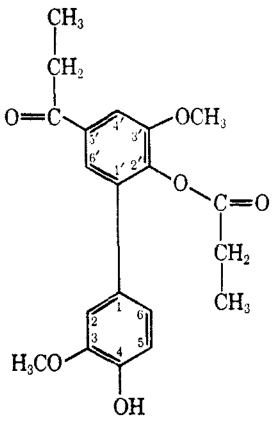
Chart II



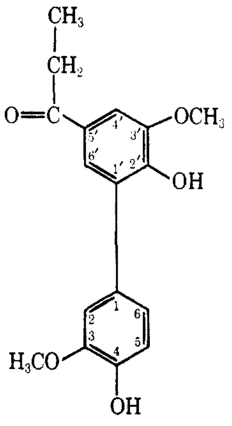
10



11



12



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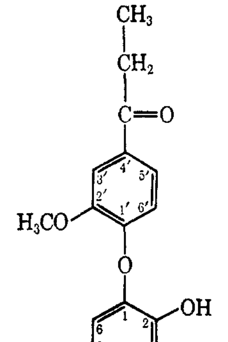

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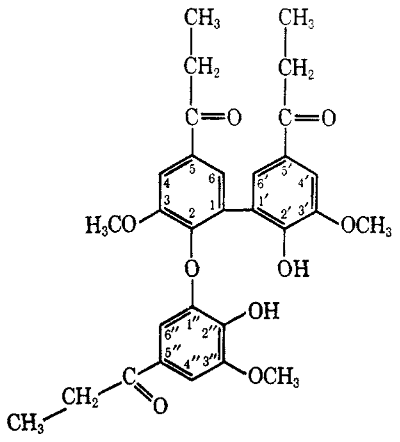

15

The ester function in **11** was established as being on the terminal ring with the *o,p'*-biphenyl linkage by the following series of experiments. The compound was methylated with diazomethane and analysis showed two added methoxyls. Reductions of the α-keto groups with $NaBH_4$, followed by ester hydrolysis, gave a product which then gave a positive test with quinone monochloroimide for free *p*-hydroxybenzyl alcohols.[8] The ester must therefore have protected the phenolic hydroxyl on either terminal ring from methylation. However, we have found that *p*-hydroxybenzyl alcohols with the *o,o'*-dihydroxybiphenyl linkage do not give this test in the normal manner,[3] and for this reason we assign the ester to the terminal ring with the *o,p'*-dihydroxybiphenyl linkage. This is supported by the proposed mechanism of formation of this compound, which involves esterification through intramolecular nucleophilic attack and side chain transfer,[5] and by the presence of the corresponding dimer **12** in the reaction mixture.

The formation of esters through side chain transfer was also demonstrated through infrared spectra on the dehydrogenation products of vanillin (**16**), acetoguaiacone (**17**), and ethyl vanillate (**18**), and thus the reaction appears to be of a general nature.[5] Propiosyringone (**19**) also gives a dehydrogenation product which shows an aliphatic ester band in the infrared spectrum, but here the mechanism must be different since there is no free *ortho* position to form an *o,p'*-biphenyl linkage. With α-(2-methoxyphenoxy)-4'-hydroxy-3'-methoxypropiophenone (**20**) definite absorption took place in the ester region but the peak was partially obscured by neighboring absorption at higher wavelengths. A similar situation existed with the corresponding β-hydroxy compound **21** but the intensity

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(6) R. B. Jackson, *J. Chromatogr.*, **16**, 306 (1964).

(7) R. Taborsky, *Anal. Chem.*, **36**, 1663 (1964).

(8) J. Gierer, *Acta. Chem. Scand.*, **8**, 1319 (1954).

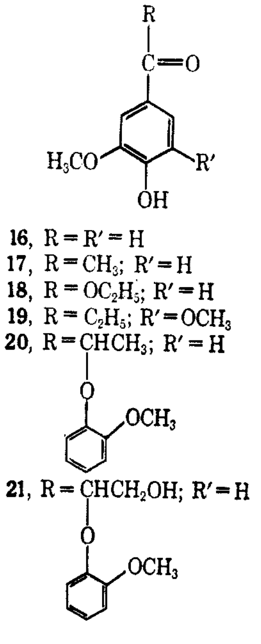
TABLE I

NMR VALUES OF COMPOUNDS 11–15[a]

Protons	11		12		13
Aromatic	7.64, d, 2, $J = 1.8$ Hz		7.58, s, 2		7.63, d, 1, $J = 1.8$ Hz
	7.58, d, 2, $J = 1.8$ Hz		6.98, s, 3		7.52, d, 1, $J = 1.8$ Hz
	7.10, d, 2, $J = 1.8$ Hz				7.16, d, 1, $J = 1.8$ Hz
					7.05, d, 2, $J = 1.8$ Hz
$-OCH_3$	3.97, s, 3		3.90, s, 3		3.98, s, 3
	3.93, s, 3		3.87, s, 3		3.93, s, 3
	3.90, s, 3				
$-CH_2-$					
C-5	3.00, m, 2, $J = 7.3$ Hz	C-5′	3.02, m, 2, $J = 7.3$ Hz	C-5′	2.98, m, 2, $J = 7.3$ Hz
C-5″	2.89, m, 2, $J = 7.3$ Hz				
C-2	2.5, m, 2, $J = 7.3$ Hz	C-2′	2.47, m, 2, $J = 7.3$ Hz		
CH_3					
C-5 C-5″	1.22, t, 6, $J = 7.3$ Hz	C-5′	1.22, t, 3, $J = 7.3$ Hz	C-5′	1.22, t, 3, $J = 7.3$ Hz
C-2	1.13, t, 3, $J = 7.3$ Hz	C-2′	1.13, t, 3, $J = 7.3$ Hz		
$-OH$	5.5–6.0 (broad)		5.92, s, 1 (broad)		

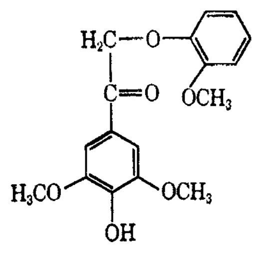
Protons	14		15
Aromatic	7.66, d, 1, $J = 1.8$ Hz		7.77, s, 2
	7.45, d, 1, $J = 1.8$ Hz		7.53, d, 1, $J = 2.0$ Hz
	7.38, m, 1, $J = 8.6$ Hz		7.47, d, 1, $J = 2.0$ Hz
	7.31, d, 1, $J = 1.8$ Hz		7.25, d, 1, $J = 2.0$ Hz
	6.84, d, 1, $J = 8.6$ Hz		6.90, d, 1, $J = 2.0$ Hz
CH_3O-	3.98, s, 3		3.89, 3, s
	3.95, s, 3		3.84, 6, s
$-CH_2-$			
C-4′	2.97, m, 2, $J = 7.3$ Hz	C-5	3.01, m, 2, $J = 7.3$ Hz
C-5	2.87, m, 2, $J = 7.3$ Hz	C-5″	2.90, m, 2, $J = 7.5$ Hz
		C-5′	2.82, m, 2, $J = 7.5$ Hz
$-CH_3-$			
C-4′	1.22, t, 3, $J = 7.3$ Hz	C-5	1.10, t, 3, $J = 7.3$ Hz
C-5	1.17, t, 3, $J = 7.3$ Hz	C-5″ C-5′	0.99, t, 6, $J = 7.5$ Hz
$-OH$	7.10, s, 1 (broad)		9.65, s, 1 (broad)
			9.52, s, 1 (broad)

[a] Recorded on Varian A60 and A60A spectrometers. Chemical shifts are given as δ values. All nmr spectra were recorded in $CDCl_3$ with Me_4Si internal standard except 13 which was recorded in $(CD_3)_2SO$.

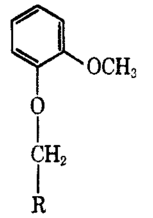


16, $R = R' = H$
17, $R = CH_3$; $R' = H$
18, $R = OC_2H_5$; $R' = H$
19, $R = C_2H_5$; $R' = OCH_3$
20, $R = CHCH_3$; $R' = H$
21, $R = CHCH_2OH$; $R' = H$

of absorption was considerably lower in this case. In both instances it appears that part of the side chain is eliminated as the free carboxylic acid. In fact, aqueous sodium bicarbonate extracts of the dehydrogenation products yield, on acidification, substances which showed definite infrared absorption in the carboxylic acid region. Side chain cleavage with carboxylic acid formation has recently been found to take place when α-guaiacoxyacetosyringone (22) was treated with white and brown rots, and purified laccase; the acid cleavage product was identified as guaiacoxyacetic acid (23), which is reduced to guaiacoxyethanol (24) in the fungal media.[9]



22



23, $R = COOH$
24, $R = CH_2OH$

The presence of o,o'-dihydroxybiphenyl linkages in lignin has been well established by spectral means,[10,11] through the isolation of dehydrodivanillin after alkaline nitrobenzene oxidation of lignin,[12] and through the isolation of dehydrodiveratric acid from alkaline $KMnO_4$ oxidation of methylated lignin.[13] However, in the recent schematic formula for lignin[14] there is no

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(9) T. K. Kirk, J. M. Harkin, and E. B. Cowling, *Biochem. Biophys. Acta*, in press.

(10) J. C. Pew, *Nature*, **193**, 250 (1962).

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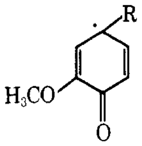
(12) J. C. Pew, *J. Amer. Chem. Soc.*, **77**, 2831 (1955).

(13) K. Freundenberg, W. Lautsch, and G. Piazolo, *Chem. Ber.*, **74**, 1879 (1941).

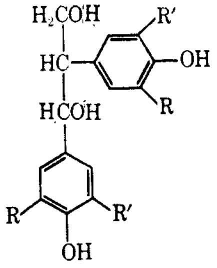
(14) K. Lundquist and G. Miksche, *Tetrahedron Lett.*, **25**, 213 (1965).

mention of the *o,p*′-oriented biphenyl linkage, and we suggest that this could be an important biaryl linkage in lignin. This could also serve to demonstrate that the cyclohexadienone type of radical **25** plays a more important part in lignification than had previously been thought.

Side chain cleavages involving such radicals have been postulated from the isolation of 4,4′-dihydroxy-3,3′-dimethoxystilbene from the acidolysis of lignin[14] and the detection of 1,2-bis(4-hydroxy-3,5-dimethoxyphenyl)propane-1,3-diol (**26**) after the mild hydrolysis of preextracted beechwood powder.[15,16] The isolation of 1,2-bis(4-hydroxy-3-methoxyphenyl)propane-1,3-diol (**27**) from spruce lignin gives evidence of the same type of reaction during lignification in conifers.[17] Recently, methylglyoxal has been isolated from the acidolysis products of lignin.[18] This is believed to indicate the presence of glyceraldehyde 2-aryl ether structures in the original substance.



25



26, R = R′ = OCH_3
27, R = H; R′ = OCH_3

Ester groups in lignin have been reported,[19] but have generally been considered to be a component of the extractives of the plant, or, if in the lignin, to be the results of secondary esterification of the lignin with *p*-hydroxycinnamic acids as has been shown to be the case with milled wood lignin from grass.[20] Our experiments suggest that esters of aliphatic acids could be an intrinsic portion of the lignin molecule. Recent infrared spectral studies of milled wood lignins have indicated that part of the absorption is due to nonconjugated ester groups.[21]

Experimental Section

All uv spectra were recorded on a Beckmann DK-2 in 95% EtOH. The general dehydrogenation procedure used in these experiments is given for **1** below and followed with other compounds.

Preparation of 4-Hydroxy-3-methoxypropiophenone (Propioguaiacone) (1).—This compound was prepared by the Fries reaction with guaiacol propionate. The compound was recrystallized from $CHCl_3$: mp 59-60° (lit.[22] mp 62-63°); uv max 302 mμ (ε 8.44 × 10^3), 274.5 (1.01 × 10^4); ir (KBr disk) 1675 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.77; H, 6.79.

Dehydrogenation of 1 and Isolation of 4,4′-Dipropionyl-6,6′-biguaiacol (10).—**1** (10 g, 0.055 mol) was dissolved in 1500 ml of hot H_2O and the solution cooled to 30°, 100 ml of H_2O containing 25 mg of horseradish peroxidase was added, and then with vigorous stirring 31.5 ml of 3% H_2O_2 (0.0275 mol) was added dropwise over a period of 30 min. Stirring was continued for another 30 min after addition of peroxide and the mixture was allowed to stand for 30 min when it was filtered. Much of excess **1** remained in the aqueous phase. The filter cake was resuspended in 1500 ml of H_2O, stirred for 3 days, and then filtered. This extracted most of the remaining **1** into the aqueous phase. The filter cake was air dried and then suspended in 50 ml of a 1:1 benzene-hexane mixture for 1 hr, filtered, and washed with 50 ml of the same solvent. This dissolved the dehydrogenation resin from crude biphenyl **12** and the resin was isolated by evaporating the solvent. **12** was purified by recrystallization from EtOAc: mp 207-208°; uv max 283 mμ (ε 2.08 × 10^4).

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 67.29; H, 6.12.

Isolation and Estimation of Amounts of Compounds from the Dehydrogenation Resin of 1.—Compounds **11**, **12**, **14**, and **15** were isolated from the dehydrogenation resin of **1** through preparative tlc on commercial 2000-μ silica GF plates,[23] or on 1000-μ silica GF plates prepared in our laboratory. The general procedure used has previously been published.[24] The solvent used was 200:5 $CHCl_3$-EtOH and the plates were developed, air dried, and then redeveloped. This process was repeated two to four times a plate and resulted in good band separation. The bands were visualized under a 2537-Å uv lamp and scraped from the plates and the compounds were eluted from the absorbents with 1:1 $CHCl_3$-EtOH. The compounds were repurified in the same manner. The amounts of the various compounds in the dehyrogenation resin were determined by quantitative tlc by a method previously reported.[25]

4′,2″-Dihydroxy-5,5″-dipropionyl-2-propionoxy-3,5′,3″-trimethoxyterphenyl (11) was isolated as a powder after preparative tlc by dripping an acetone solution of the compound into hexane and filtering the resulting precipitate: uv max 252.2 mμ (ε 3.53 × 10^4); ir (KBr disk) 1675 (C=O) and 1770 cm^{-1} (ester C=O).

Anal. Calcd for $C_{30}H_{32}O_9$: C, 67.15; H, 6.02. Found: C, 67.10; H, 6.25.

3,3′-Dimethoxy-4-hydroxy-2′-propionoxy-5′-propionylbiphenyl (12) was isolated as a resin after preparative tlc: uv max 253.3 mμ (ε 1.86 × 10^4); ir (film) 1675 (C=O) and 1770 cm^{-1} (ester C=O).

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 66.82; H, 6.40.

2-Hydroxy-3-methoxy-5-propionylphenyl 2′-methoxy-4′-propionylphenyl ether (14) was isolated as a resin after preparative tlc: uv max 294.3 mμ (ε 1.72 × 10^4) and 276.1 (1.88 × 10^4); ir film 1786 (ester C=O) and 1675 cm^{-1} (C=O). After $NaBH_4$ reduction **14** gave the dibenzyl alcohol compound with uv max 278.5 mμ (ε 4.44 × 10^3) and 275.5 (4.52 × 10^3), which is identical with the uv spectrum of the diphenyl ether with the saturated side chains.[3]

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 67.10; H, 6.29.

3,3′-Dimethoxy-2′-hydroxy-5,5′-dipropionylbiphenyl-2-yl 2″-hydroxy-3″-methoxy-5″-propionylphenyl ether (15) was crystallized from acetone: mp 235-236°; uv max 283.8 mμ (ε 2.56 × 10^4); ir (KBr disk) 1675 cm^{-1} (C=O). After reduction with $NaBH_4$, **15** gave the tribenzyl alcohol compound with uv max 281.7 mμ (ε 6.18 × 10^3) which is nearly identical with the uv spectrum of the triphenyl compound with saturated side chains.[3]

Anal. Calcd for $C_{30}H_{32}O_9$: C, 67.15; H, 6.02. Found: C, 67.05; H, 5.96.

Vanillin (16), **acetoguaiacone (17)**, and **ethyl vanillate (18)** are commercially available and were used in the dehydrogenation reactions as purchased.

4-Hydroxy-3,5-dimethoxypropiophenone (19) was synthesized in the same manner as **1** but the Perrier complex did not separate from the reaction mixture, thus necessitating the following

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[15] H. Nimz, *Chem. Ber.*, **98**, 533 (1965).

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[17] K. Freudenberg, C-L. Chen, J. M. Harkin, H. Nimz, and H. Renner, *Chem. Commun.*, **224** (1965).

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[19] D. C. C. Smith, *J. Chem. Soc.*, 2347 (1955).

[20] T. Higucki, Y. Ito, M. Shimada, and I. Kawamura, *Phytochem.*, **6**, 1551 (1967).

[21] K. V. Sarkanen, H.-M. Chang, and G. G. Allen, *Tappi*, **50**, 583 (1967).

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[23] Analtech. Inc., Wilmington, Del.

[24] M. K. Seikel, M. A. Millett, and J. F. Saeman, *J. Chromatogr.*, **15**, 115 (1964).

[25] M. A. Millett, W. E. Moore, and J. F. Saeman, *Anal. Chem.*, **36**, 491 (1964).

changes. The nitrobenzene reaction mixture was dumped into ice-H_2O and this mixture extracted with ether. The ether layer was extracted with aqueous NaOH, the NaOH extract acidified, and a solid product precipitated. The product (10.1 g, 20.2%) was recrystallized from cyclohexane: mp 109–110° (lit.[26] mp 109–110°); uv max 299 mμ (ε 1.12×10^4); ir (KBr disk) 1660 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.61; H, 6.88.

α-(2-Methoxyphenoxy)-4-hydroxy-3-methoxypropiophenone (**20**) was synthesized from the benzyl ether of **1** by a previously described method[27] then debenzylated by warming 2 g of the benzyl ether of **20** with 10 ml of HOAc and 5 ml of HCl for 20 min in the steam bath. The product was crystallized from EtOAc–hexane: mp 133–135°; uv max 308 mμ (ε 5.42×10^4) and 279.5 (6.29×10^4); ir (KBr disk) 1675 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.53; H, 6.03. Found: C, 67.52; H, 6.19.

α-[(2-Methoxyphenoxy)-β-hydroxy]-4-hydroxy-3-methoxypropiophenone (**21**) was synthesized as the benzyl ether according to previously published report for the corresponding dimethoxy (veratryl) compound,[27] then debenzylated by hydrogenolysis over $PdCl_2/C$:[28] mp 80–82°; uv max 309.6 mμ (ε 1.2×10^5) and 279.6 (1.32×10^5); ir 1675 cm^{-1} (C=O).

Propionic Acid Determination.—The acid was obtained by steam distillation of an acidified saponification mixture from the dehydrogenation of **1**. The acid was extracted from the steam distillate with ether and identified by glpc on a 1.95 × 0.25 in. stainless steel column packed with 20% sebacic acid on acid-washed Chromosorb W.[6] The acid was also converted into the 5-methoxytripytamine salt, mp 114–115°, mp 114–115°, with a derivative from reagent propionic acid.

Registry No.—**1**, 1835-14-9; **10**, 18592-97-7; **11**, 16737-80-7; **12**, 18592-99-9; **13**, 18593-00-5; **14**, 16737-81-8; **15**, 18593-02-7; **19**, 5650-43-1; **20**, 7107-93-9.

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[28] A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, John Wiley & Sons, Inc., New York, N. Y., 1962, p 950.

Hydrogen–Deuterium Exchange of the Thiapyrones, N-Methylpyridones, and N-Methylpyrimidones in Basic Media

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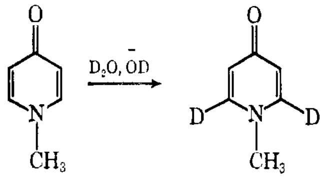
Base-catalyzed hydrogen–deuterium exchange occurs at the positions adjacent to the heteroatom for 4-thiapyrone (**3**), N-methyl-2-pyridone (**9**), 4-methoxy-N-methylpyridinium fluoroborate (**19**), and 1,3-dimethyl-4-pyrimidonium fluoroborate. The rates of exchange, relative to that of N-methyl-4-pyridone (**1**) in deuterium oxide at 100°, are for **3**, $10^{4.8}$ (deuterium oxide at 100°); **9**, $10^{-0.8}$ (deuterium oxide at 100°); and **19**, $10^{5.3}$ (deuteriomethanol at 40°). Attempts to observe isotopic exchange at the corresponding positions in 2-thiapyrone, 2-pyrone and 4-pyrone led to substrate decomposition. Hydrogen–deuterium exchange at the 2 position of 3-methyl-4-pyrimidone and 1-methyl-4-pyrimidone in deuterium oxide at 100° is zero order in base as previously reported.[6] These results are interpreted qualitatively in terms of ylide intermediates.

Following the discovery that N-methyl-4-pyridone (**1**) undergoes base-catalyzed hydrogen–deuterium exchange at 100° in deuterium oxide to give N-methyl-4-pyridone-2,6-d_2 (**2**) by an ylide mechanism,[1] a systematic study was undertaken of the effect of the position and type of heteroatom on exchange. The goals of this work were to determine the scope of the reaction and to compare the rates of exchange with analogous reactions of structurally related five-membered[2,3] and six-membered[4–6] heteroaromatics.[7] This information should provide a guide for the synthetic use of the ylide intermediates.



1 **2**

Studies of the six-membered mesoionic heteroaromatics containing one nitrogen, sulfur or oxygen atom, of the 4-pyrimidones, and of some pyridinium salts are reported herein. These results suggest that the formation of ylides is an important reaction pathway for six-membered mesoionic or cationic sulfur and nitrogen heteroaromatic.

Results

The positions and rates of hydrogen–deuterium exchange in the compounds studied were determined by

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