present research the substance was found to mutarotate slowly in U. S. P. chloroform although not appreciably in dry (*i.e.*, alcohol-free) chloroform, the initial rotation varying with different samples. For this reason, the equilibrium rotation of the compound in 18:7 dioxane–water was found to be the most convenient physical constant. At a concentration of approximately 4 in this solvent mixture initial specific rotations ranging from +32.0 to +35.4° were obtained. When a drop of aqueous ammonia or of 6 *N* hydrochloric acid was added the rotation fell rapidly to a constant value of +23.4°. Several crystallizations from aqueous alcohol of the nearly pure product initially obtained gave material showing the above equilibrium rotation; further recrystallizations failed to change this value.

The Rate of Reaction of Tribenzoyl-α-D-xylopyranosyl Bromide with 18:7 Dioxane–Water (v./v.) at 20°.—Tribenzoyl-α-D-xylofuranosyl bromide (0.2820 g.) was dissolved in 18.0 ml. of dioxane and the solution made up to a volume of 25.0 ml. with water. Data obtained by polarimetric observation of the solution at 20° in a 1.5-dm. tube are plotted in Fig. 1. The observed rotation was constant at +0.35° after 2 days.

Catalytic Reduction of 2,3,4-Tribenzoyl-α-D-xylose.—Attempts to reduce 2,3,4-tribenzoyl-α-D-xylose at room temperature and under 2200 p.s.i. of hydrogen either with platinum black suspended in methanol or Raney nickel in 1:1 dioxane–alcohol failed. Five grams of 2,3,4-tribenzoyl-D-xylose with *ca.* 0.5 g. of Raney nickel was suspended in absolute alcohol (total volume 25 ml.) and agitated at 118° for 50 minutes under 2200 p.s.i. of hydrogen. The clear, colorless solution from which the catalyst had been removed showed a specific rotation of +2.09°, probably indicating that the reaction was incomplete; a Fehling test, however, appeared to be negative. A sample of the sirup which was obtained on removal of solvent was benzoylated with benzoyl chloride and pyridine in the usual manner to give a product which remained amorphous even when seeded with authentic xylitol pentabenzoate. This amorphous material was returned to the main batch and the whole debenzoylated with methanolic barium methoxide in the usual fashion. From alcohol the product crystallized as clear prisms (1.06 g., 64%) melting at 94–96° either alone or in admixture with authentic xylitol. Benzoylation of 0.5 g. of the product afforded 1.97 g. (90%) of crystalline material melting at 106–108°; a mixed melting point with authentic xylitol pentabenzoate was undepressed.

Acknowledgment.—We wish to thank Mr. Harry W. Diehl for assistance in certain of the preparations.

BETHESDA, MARYLAND

[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Reactions of Vanillin and its Derived Compounds. XXI.[1] Amides of Vanillic and 3-Ethoxy-4-hydroxybenzoic Acids[2,3]

BY IRWIN A. PEARL AND DONALD L. BEYER

RECEIVED JANUARY 14, 1953

N-Substituted amides of vanillic acid and 3-ethoxy-4-hydroxybenzoic acid were prepared by condensing the O-carbethoxy chlorides of these acids with the appropriate amines and selectively hydrolyzing the O-carbethoxy group of the resulting O-carbethoxyamides. The compounds were tested for activity against *Bacillus mycoides* and a large number of pathogenic bacteria and fungi. In general, the activity was poor and, unlike the esters of these acids, the substituted amides of vanillic acid exhibited greater activity than did the corresponding amides of 3-ethoxy-4-hydroxybenzoic acid.

During the past several years esters of vanillic acid have been employed in the treatment of systemic fungus diseases.[4,5] Effective therapeutic levels could be obtained only by massive oral doses and thus the margin between therapeutic doses and those which produced toxic manifestations was not as large as desired. Because the necessary massive oral doses were due presumably to the fact that the esters of vanillic acid hydrolyzed relatively rapidly in the body and because it was known that the amide linkage is more stable toward hydrolysis in the body than is the ester linkage, it was thought that substituted amides of vanillic acid might possess more prolonged antifungal or antibacterial activity when administered systemically. Accordingly, a number of N-substituted amides of vanillic acid and the closely related 3-ethoxy-4-hydroxybenzoic acid were prepared and tested for their antibacterial and antifungal activity.

A number of years ago, during the preparation of certain esters of vanillic acid by the use of carbethoxy intermediates,[6] three amides of vanillic acid—namely, vanillamide, N-phenylvanillamide and N-2-pyridinovanillamide—were prepared by treating carbethoxyvanilloyl chloride with the desired amine and partially hydrolyzing the carbethoxyvanillamide thus obtained. Ritter[7] prepared vanillamide by pyrolysis of butyl vanillimidate hydrochloride and Kratzl and Kvasnicka[8] prepared several N-substituted amides of vanillic acid through either their carbethoxy or acetyl intermediates. The N-substituted vanillamides and 3-ethoxy-4-hydroxybenzamides of this paper were prepared *via* their O-carbethoxy intermediates.

The N-substituted-O-carbethoxyvanillamides and O-carbethoxy-3-ethoxy-4-hydroxybenzamides were prepared by treating the desired amine with the O-carbethoxyacid chloride in a boiling mixture of pyridine and ether or in ether solution at room temperature or below depending upon the volatility of the amine. The carbethoxy intermediates were converted to their respective vanillamides or 3-ethoxy-4-hydroxybenzamides by selective hydrolysis of the carbethoxy group in *N* sodium hydroxide or methanol and sodium hydroxide at room temperature.

(1) For paper XX of this series, see THIS JOURNAL, **74**, 4593 (1952).

(2) Presented before the Division of Medicinal Chemistry at the 123rd Meeting of the American Chemical Society, Los Angeles, California, March 15–19, 1953.

(3) This paper represents a portion of the results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Research League and conducted for the League by The Institute of Paper Chemistry. Acknowledgment is made by the Institute for permission on the part of the League to publish these results.

(4) A. Christie, J. G. Middleton, J. C. Peterson and D. L. McVicker, *Pediatrics*, **7**, 7 (1951).

(5) R. Cohen, *Arch. Pediat.*, **68**, 259 (1951).

(6) I. A. Pearl and J. F. McCoy, THIS JOURNAL, **69**, 3071 (1947).

(7) D. M. Ritter, *ibid.*, **68**, 2738 (1946).

(8) K. Kratzl and E. Kvasnicka, *Monatsh.*, **83**, 18 (1952).

TABLE I

N-SUBSTITUTED-O-CARBETHOXY VANILLAMIDES AND 3-ETHOXY-4-HYDROXYBENZAMIDES

Substituent	Method of prepn.	Yield, %	M.p.,[a] °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
				Vanillamides				
Isopropyl	II	100	94–95	$C_{14}H_{19}O_5N$	59.77	60.03	6.81	6.80
Propyl	II	100	79–80	$C_{14}H_{19}O_5N$	59.77	60.08	6.81	6.81
Isobutyl	I	97	99.5–100	$C_{15}H_{21}O_5N$	61.00	61.10	7.17	7.15
Butyl	I	94	70–71	$C_{15}H_{21}O_5N$	61.00	61.06	7.17	7.15
s-Butyl	I	100	95–96	$C_{15}H_{21}O_5N$	61.00	61.18	7.17	7.20
Amyl	I	100	75–76	$C_{16}H_{23}O_5N$	62.12	62.11	7.49	7.47
Isoamyl	I	100	70–71	$C_{16}H_{23}O_5N$	62.12	61.76	7.49	7.44
Hexyl	I	82	61–62	$C_{17}H_{25}O_5N$	63.14	63.12	7.79	7.81
Heptyl	I	98	69–70	$C_{18}H_{27}O_5N$	64.07	64.17	8.07	8.04
2-Ethylhexyl	I	100	[b]	$C_{19}H_{29}O_5N$	64.93	64.87	8.32	8.47
Benzyl	I	99	115–116	$C_{18}H_{19}O_5N$	65.64	65.95	5.82	5.82
Dibutyl	I[c]	98	[d]	$C_{19}H_{29}O_5N$	64.93	64.78	8.32	8.32
				3-Ethoxy-4-hydroxybenzamides				
Ethyl	II	95	100–101	$C_{14}H_{19}O_5N$	59.77	59.87	6.81	6.74
Isopropyl	II	100	113–114	$C_{15}H_{21}O_5N$	61.00	61.15	7.17	7.16
Propyl	II	100	89–90	$C_{15}H_{21}O_5N$	61.00	61.12	7.17	7.14
Isobutyl	II[e]	100	99–100	$C_{16}H_{23}O_5N$	62.12	62.25	7.49	7.55
Butyl	II[e]	100	74–75	$C_{16}H_{23}O_5N$	62.12	62.22	7.49	7.65
s-Butyl	I	100	93–94	$C_{16}H_{23}O_5N$	62.12	62.05	7.49	7.49
Isoamyl	I	100	88–89	$C_{17}H_{25}O_5N$	63.14	62.86	7.79	7.78
Amyl	I	100	65–66	$C_{17}H_{25}O_5N$	63.14	62.65	7.79	7.69
Hexyl	I	100	52–54[f]	$C_{18}H_{27}O_5N$	64.07	63.89	8.07	8.02
Heptyl	I	100	64–65	$C_{19}H_{29}O_5N$	64.93	64.41	8.32	8.22
2-Ethylhexyl	II[g]	90	67–68[h]	$C_{20}H_{31}O_5N$	65.72	65.85	8.55	8.56
Benzyl	II[e]	100	90–91	$C_{19}H_{21}O_5N$	66.46	66.45	6.16	6.26
Diisopropyl	II[g]	88	61–62	$C_{18}H_{27}O_5N$	64.07	63.98	8.07	8.04
Dibutyl	II[g]	93	[i]	$C_{20}H_{31}O_5N$	65.72	65.73	8.55	8.30

[a] All compounds were recrystallized from petroleum ether (b.p. 65–110°). [b] B.p. 212–216° (0.4 mm). [c] Product isolated by ether extraction. [d] B.p. 198–201° (0.5 mm.). [e] Reactants mixed at 12°. [f] B.p. 216° (0.8 mm.). [g] Reactants mixed at 20°. [h] B.p. 225° (0.9 mm.). [i] B.p. 205° (0.7 mm.), $n^{27}D$ 1.5207.

Data for the O-carbethoxy intermediates and for the N-substituted amides are given in Tables I and II, respectively. The ultraviolet absorption spectra of the amides of vanillic and 3-ethoxy-4-hydroxybenzoic acids were determined in purified 95% ethanol with a Beckman spectrophotometer at minimum slit width. These spectra were almost identical with those of the corresponding esters of vanillic acid,[9,10] possessing maxima at 290, 260, and 220 mμ and minima at 280 and 235 mμ.

The minimal inhibiting concentrations of these amides were determined for the bacteria *Bacillus mycoides, Staphylococcus aureus, Klebsiella pneumoniae,* and B.C.G. strain of *Mycobacterium tuberculosis* and for the fungi *Aspergillus fumigatus, Aspergillus niger, Alternaria solani, Botrytis cinerea, Candida albicans, Microsporum audouini, Penicillium notatum, Rhodotorula glutinis, Saccharomyces cerevisiae, Trichophyton mentagrophytes,* and *Fusarium bulbigenum.* Data are given in Table II for *Bacillus mycoides.*

The inhibiting concentrations of these amides for the pathogenic microörganisms were in almost all cases too high to be of interest. The heptyl amide of both vanillic acid and 3-ethoxy-4-hydroxybenzoic acid appeared to be the most generally effective in both series. It is obvious that, whereas the esters of 3-ethoxy-4-hydroxybenzoic acid are more effective against representative microörganisms than are the corresponding esters of vanillic acid,[6,9,11] just the reverse holds true for the substituted amides of these acids.

Experimental

All melting points given are uncorrected.

O-Carbethoxy-3-ethoxy-4-hydroxybenzoic Acid.—A solution of 182 g. (1.0 mole) of 3-ethoxy-4-hydroxybenzoic acid[11] in a solution of 80 g. (2.0 moles) of sodium hydroxide in 2000 cc. of water was treated dropwise with vigorous stirring with 119 g. (1.1 moles) of ethyl chlorocarbonate. After addition was complete the mixture was stirred 30 minutes and then slowly acidified with dilute hydrochloric acid to *p*H 7. The oily scum which separated was filtered, and the clear filtrate was strongly acidified with more acid. The oil which separated solidified after a few minutes of vigorous stirring. The solid was filtered, washed, dried and recrystallized from petroleum ether (b.p. 65–110°) to give 231 g. (91%) of O-carbethoxy-3-ethoxybenzoic acid melting at 105–106°.

Anal. Calcd. for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.94; H, 5.52.

O-Carbethoxyacid Chlorides.—O-Carbethoxyvanilloyl chloride was prepared by the method of Heap and Robinson[12] by treating O-carbethoxyvanillic acid with excess thionyl chloride and removing the excess under reduced pressure. The oily residue was purified by solution in hot petroleum ether (b.p. 65–110°), filtering, and removing the petroleum ether under reduced pressure.

O-Carbethoxy-3-ethoxy-4-hydroxybenzoyl chloride was prepared in the same manner and was obtained as an almost colorless oil.

(9) I. A. Pearl, THIS JOURNAL, **71**, 2331 (1949).

(10) I. A. Pearl and D. L. Beyer, *ibid.*, **73**, 4091 (1951).

(11) I. A. Pearl and D. L. Beyer, *ibid.*, **74**, 3188 (1952).

(12) T. Heap and R. Robinson, *J. Chem. Soc.*, 2336 (1926).

TABLE II

N-SUBSTITUTED VANILLAMIDES AND 3-ETHOXY-4-HYDROXYBENZAMIDES

Substituent	Method of prepn.	Yield, %	M.p.,[a] °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Inhibiting concn., mg./ml. *Bacillus mycoides*
Vanillamides									
Isopropyl	III[b]	75	148–149	$C_{11}H_{15}O_3N$	63.14	63.22	7.23	7.17	1.5
Propyl	III[c]	80	[d]	$C_{11}H_{15}O_3N$	63.14	63.23	7.23	7.26	0.9
Isobutyl	III	88	112–113	$C_{12}H_{17}O_3N$	64.55	64.56	7.68	7.65	1.5
Butyl	III	90	98–99	$C_{12}H_{17}O_3N$	64.55	64.60	7.68	7.66	0.9
s-Butyl	III	85	151–152	$C_{12}H_{17}O_3N$	64.55	64.63	7.68	7.67	1.5
Amyl	III	85	110–111	$C_{13}H_{19}O_3N$	65.80	65.80	8.07	8.06	0.9
Isoamyl	III	90	123–124	$C_{13}H_{19}O_3N$	65.80	65.75	8.07	8.08	1.5
Hexyl	III	90	104–105	$C_{14}H_{21}O_3N$	66.90	67.03	8.42	8.41	0.9
Heptyl	III	85	67–69[e]	$C_{15}H_{23}O_3N$	67.89	67.42	8.74	8.71	0.09
2-Ethylhexyl	IV	80	[f]	$C_{16}H_{25}O_3N$	68.78	68.57	9.02	8.87	0.09
Nonyl	III	65[g]	152–153	$C_{17}H_{27}O_3N$	69.59	69.48	9.28	9.23	1.5
Benzyl	III	85	167–168	$C_{15}H_{15}O_3N$	70.02	70.06	5.88	5.88	1.5
Dibutyl	IV	90	[h]	$C_{16}H_{25}O_3N$	68.78	68.37	9.02	8.93	0.3
3-Ethoxy-4-hydroxybenzamides									
Ethyl	III[i]	90	156–157	$C_{11}H_{15}O_3N$	63.14	63.09	7.23	7.16	>2.1
Isopropyl	III[j]	85	166–167	$C_{12}H_{17}O_3N$	64.55	64.36	7.67	7.64	>2.1
Propyl	III[g]	85	115–116	$C_{12}H_{17}O_3N$	64.55	63.91	7.67	7.67	>2.1
Isobutyl	III[c]	85	114–115	$C_{13}H_{19}O_3N$	65.80	65.64	8.07	7.98	1.5
Butyl	III	90	118–119	$C_{13}H_{19}O_3N$	65.80	65.95	8.07	8.17	>2.1
s-Butyl	III	65	157–158	$C_{13}H_{19}O_3N$	65.80	65.62	8.07	8.07	>2.1
Isoamyl	III	90	128–129	$C_{14}H_{21}O_3N$	66.90	66.94	8.42	8.42	>2.1
Amyl	III	90	122–123	$C_{14}H_{21}O_3N$	66.90	66.95	8.42	8.38	>2.1
Hexyl	III	85	115–116	$C_{15}H_{23}O_3N$	67.89	67.90	8.74	8.74	>2.1
Heptyl	IV	80	79–80[k]	$C_{16}H_{25}O_3N$	68.78	68.43	9.02	8.99	>2.1
2-Ethylhexyl	IV	85	[l]	$C_{17}H_{27}O_3N$	69.59	69.52	9.28	9.29	>2.1
Benzyl	III[c]	90	125–126	$C_{16}H_{17}O_3N$	70.82	70.85	6.32	6.27	>2.1
Diisopropyl	IV	90	142–143	$C_{15}H_{23}O_3N$	67.89	67.89	8.74	8.76	1.5
Dibutyl	IV	85	77–78	$C_{17}H_{27}O_3N$	69.59	69.64	9.28	9.19	0.21

[a] All compounds recrystallized from dilute ethanol in presence of decolorizing carbon. [b] Hydrolyzed for 30 minutes. [c] Hydrolyzed for 2 hours. [d] B.p. 182–185° (0.3 mm.). [e] B.p. 205–207° (0.4 mm.). [f] B.p. 206–207° (0.7 mm.). [g] This yield is based upon the original O-carbethoxyvanilloyl chloride because the intermediate O-carbethoxyamide could not be isolated in pure form. [h] B.p. 176–180° (0.6 mm.). [i] Hydrolyzed for 3 hours. [j] Hydrolyzed for 5 hours. [k] B.p. 233° (2.4 mm.). [l] B.p. 211° (0.9 mm.).

O-Carbethoxyvanillamide.—An ether solution of O-carbethoxyvanilloyl chloride was saturated with anhydrous ammonia. The white precipitate was filtered and recrystallized from ethanol or water to give O-carbethoxyvanillamide as white crystals melting at 160–161°.

Anal. Calcd. for $C_{11}H_{13}O_5N$: C, 55.22; H, 5.48. Found: C, 55.28; H, 5.51.

Carbomethoxyvanillamide was prepared in the same manner from O-carbomethoxyvanilloyl chloride[13] and was obtained as white needles melting at 145–146°.

Anal. Calcd. for $C_{10}H_{11}O_5N$: C, 53.33; H, 4.92. Found: C, 53.37; H, 4.95.

N-Substituted-O-carbethoxyvanillamides and 3-Ethoxy-4-hydroxybenzamides.—These compounds were prepared by reaction of the O-carbethoxyacid chloride with either one mole of the desired amine in the presence of pyridine (method I) or with an excess of the amine in ether solution (method II).

Method I. Preparation of N-Butyl-O-carbethoxyvanillamide.—A solution of 64.5 g. (0.25 mole) of O-carbethoxyvanilloyl chloride in 200 cc. of dry ether was treated portionwise with a solution of 18 g. (0.25 mole) of butylamine and 50 cc. of ether in 80 cc. of pyridine. After addition was complete, the mixture was refluxed for 30 minutes and allowed to stand at 20° for 16 hours. The solvent was removed under reduced pressure, and the residue was stirred into 1000 cc. of cracked ice and concentrated hydrochloric acid. The crude product separated as an oil, but on recrystallization from petroleum ether (b.p. 65–110°), it yielded fluffy white needles of N-butyl-O-carbethoxyvanillamide melting at 70–71°. The analyses of this and other O-carbethoxyamides are given in Table I.

N-Butyl-O-carbomethoxyvanillamide was prepared in the same manner and was obtained as white fluffy needles melting at 78–79°.

Anal. Calcd. for $C_{14}H_{19}O_5N$: C, 59.77; H, 6.81. Found: C, 59.79; H, 6.85.

Method II. Preparation of N-Isopropyl-O-carbethoxyvanillamide.—A solution of 32 g. (0.125 mole) of O-carbethoxyvanilloyl chloride in 300 cc. of dry ether was cooled in a brine-bath to 2° and treated slowly with a cooled solution of 15 g. (0.25 mole) of isopropylamine in 50 cc. of dry ether. A crystalline precipitate of isopropylamine hydrochloride separated. The mixture was stirred one hour at 2° and then allowed to stand 16 hours at 20°. The mixture was concentrated to dryness and the residue was boiled with petroleum ether (b.p. 65–110°) and filtered. Cooling of the filtrate yielded 35 g. of N-isopropyl-O-carbethoxyvanillamide as white fluffy needles melting at 94–95°. The insoluble isopropylamine hydrochloride melted at 154–155°.

N-Substituted Vanillamides and 3-Ethoxy-4-hydroxybenzamides.—The above prepared N-substituted-O-carbethoxyamides were selectively hydrolyzed at 20° with *N* sodium hydroxide (method III) and with *N* sodium hydroxide and methanol (method IV) in those cases where the starting material was completely insoluble.

Method III. Preparation of N-Butylvanillamide.—A mixture of 12 g. of N-butyl-O-carbethoxyvanillamide and 150 cc. of *N* sodium hydroxide was stirred and allowed to stand 16 hours at 20°. The alkaline solution was filtered, and the filtrate was acidified with 1:1 hydrochloric acid. The crystalline solid was filtered and recrystallized from

(13) E. Fischer and K. Freudenberg, *Ann.*, **372**, 47 (1909).

dilute ethanol in the presence of decolorizing carbon to give colorless crystals of N-butylvanillamide melting at 98–99°. The analyses of this and other N-substituted amides are given in Table II.

Method IV. Preparation of N-Heptyl-3-ethoxy-4-hydroxybenzamide.—A solution of 50 g. of N-heptyl-O-carbethoxy-3-ethoxy-4-hydroxybenzamide in 250 cc. of methanol was treated with 250 cc. of *N* sodium hydroxide and allowed to stand 2 hours at 20°. The solution was filtered and acidified with 1:1 hydrochloric acid. The methanol was removed under reduced pressure, and the viscous oil which separated from the aqueous solution was distilled under reduced pressure to give 80% of N-heptyl-3-ethoxy-4-hydroxybenzamide as a very viscous slightly yellow oil boiling at 233° (2.4 mm.). Upon standing the product solidified to crystals melting at 79–80°.

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APPLETON, WISCONSIN

[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Reactions of Vanillin and its Derived Compounds. XXII.[1] Ethers of Protocatechuic Acid and their Ethyl Esters[2]

BY IRWIN A. PEARL AND DONALD L. BEYER

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Vanillin was demethylated to protocatechualdehyde by means of anhydrous aluminum bromide, and the aldehyde was alkylated to several of its mono- and dialkyl ethers by reaction with alkyl halide in the presence of alkali or alkali carbonate. The alkyl ethers of protocatechualdehyde were oxidized to their respective acids with one mole of silver oxide in the presence of excess aqueous alkali. Ethyl esters of these acids were prepared by reaction with anhydrous ethanol in the presence of concentrated sulfuric acid. The sulfuric acid was removed by means of anion-exchange resin. Inhibiting concentrations of these esters toward *Bacillus mycoides* indicated a slight increase in activity with increasing chain length in the ether group, but no effect caused by change in position of the ether group.

During the course of our studies on the use of vanillin as a raw material for the production of organic chemicals it was desired to demethylate vanillin to the parent protocatechualdehyde and realkylate the latter to several of its mono- and dialkyl ethers. These ethers of protocatechualdehyde were desired as intermediates for preparing their derived acids and esters for inclusion in our testing program on the inhibiting concentrations of esters of vanillic and related acids for representative microörganisms.[3-7] Indications were that increasing the molecular weight of the alkyl radical in the ether group of protocatechuic acid esters resulted in increased activity.[7]

Vanillin was demethylated easily with anhydrous aluminum bromide in nitrobenzene solution to give a good yield of protocatechualdehyde, which was alkylated with one mole of ethyl bromide and two moles of potassium hydroxide in ethanolic solution by the procedure of Bertram[8] for preparing vanillin from protocatechualdehyde. In addition to the desired 3-ethoxy-4-hydroxybenzaldehyde, some 3,4-diethoxybenzaldehyde and unchanged protocatechualdehyde were obtained. However, no 4-ethoxy-3-hydroxybenzaldehyde was formed. Similar alkylation with butyl bromide yielded a mixture of unchanged protocatechualdehyde, 3-butoxy-4-hydroxybenzaldehyde and 3,4-dibutoxybenzaldehyde. Ethyl protocatechuate was also alkylated with one mole of alkyl halide in the presence of two moles of potassium carbonate in anhydrous acetone to yield only the meta-ether. Ethyl protocatechuate was also alkylated with ethyl bromide and two moles of potassium carbonate in ethanol in accordance with the procedure reported by Sommer[9] for the preparation of vanillin from protocatechualdehyde. In this case all possible alkylation products were obtained and isolated by chromatographing from petroleum ether on acid-washed Magnesol and developing with 50:1 petroleum ether–ethanol. Thus, all ethers of protocatechuic acid become available.

Several 3-substituted and 4-substituted monoethers of protocatechualdehyde, namely, 3-isopropoxy-4-hydroxybenzaldehyde, 3-butoxy-4-hydroxybenzaldehyde, 3-*s*-butoxy-4-hydroxybenzaldehyde, 3-benzyloxy-4-hydroxybenzaldehyde, 3-hydroxy-4-methoxybenzaldehyde (isovanillin), and 4-ethoxy-3-hydroxybenzaldehyde were obtained from Monsanto Chemical Company. These aldehydes were oxidized to their respective acids by treatment with one mole of freshly prepared silver oxide in the presence of an excess of aqueous alkali.[7] Data for these acids are given in Table I. The acids were esterified with ethanol in the presence of sulfuric acid. The sulfuric acid was removed with the anion-exchange resin, Duolite A-2, in ethanolic solution, and the solution thus obtained was concentrated to dryness to yield the substantially pure ester. Data for these esters are given in Table II.

The inhibiting concentrations of these esters

(1) For paper XXI of this series, see THIS JOURNAL, **75**, 2627 (1953).

(2) This paper represents a portion of the results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Research League and conducted for the League by The Institute of Paper Chemistry. Acknowledgment is made by the Institute for permission on the part of the League to publish these results.

(3) I. A. Pearl and J. F. McCoy, THIS JOURNAL, **69**, 3071 (1947).

(4) I. A. Pearl and D. L. Beyer, *ibid.*, **71**, 1066 (1949).

(5) I. A. Pearl and D. L. Beyer, *ibid.*, **72**, 1743 (1950).

(6) I. A. Pearl and D. L. Beyer, *ibid.*, **73**, 4091 (1951).

(7) I. A. Pearl and D. L. Beyer, *ibid.*, **74**, 3188 (1952).

(8) J. Bertram, German Patent 63,007 (Aug. 19, 1890); *Ber.* **25**, R823 (1892).

(9) R. Sommer, German Patent 122,851 (May 27, 1900).