[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Reactions of Vanillin and its Derived Compounds. V.[1] Some Esters of Vanillic Acid[2]

BY IRWIN A. PEARL AND JOHN F. MCCOY

The recent development of satisfactory methods for the simple conversion of vanillin to vanillic acid[3] prompted a study of vanillic acid esters. Although ethyl vanillate was first prepared seventy years ago,[4] very little work has been reported on the esters of vanillic acid. In the course of an extensive investigation of the antimicrobic properties of hydroxy- and alkoxybenzoic acids and esters, Sabalitschka and Tietz[5] prepared several esters of vanillic acid and tested their effectiveness in preventing the fermentation of glucose by yeast. Some of these esters were further studied as food preservatives in this Laboratory.[6] The present paper reports the preparation of a number of new vanillic acid esters and the toxicity toward selected micro-organisms of these and several known esters of vanillic acid.

Except for the *t*-butyl ester, all the alkyl esters were prepared by heating vanillic acid with an excess of the corresponding anhydrous alcohol in the presence of either sulfuric or hydrochloric acid. Under either of these conditions, *t*-butyl alcohol was more susceptible to dehydration than it was to esterification and all attempts at esterification yielded only isobutylene and the original vanillic acid. Recourse was made to two indirect methods. In the first method, carbomethoxyvanilloyl chloride was condensed with *t*-butyl alcohol in pyridine and the *t*-butyl carbomethoxyvanillate was hydrolyzed to *t*-butyl vanillate. In the second procedure, *t*-butyl chloride was condensed with potassium vanillate.

Phenyl and guaiacyl vanillates were prepared *via* the carbethoxy route and also by esterification of the phenol with vanillic acid in the presence of phosphorus oxychloride.

The inhibiting concentrations of these esters were determined for three representative aerobic micro-organisms—namely, non-spore-forming (*Aerobacter aerogenes*) and spore-forming (*Bacillus mycoides*) bacteria and molds (*Aspergillus niger*). Low concentrations of most of the vanillates were found to inhibit the growth of *Bacillus mycoides* and of *Aspergillus niger*. *Aerobacter aerogenes* was uninhibited except by two butyl vanillates. The two hexyl esters studied were very specific in their action against *Bacillus mycoides*. More new esters of vanillic acid and related acids have been prepared and are being tested. The results of these tests will be reported in a future paper.

(1) For paper IV of this series see Pearl, THIS JOURNAL, **68**, 2180 (1946).

(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) See Pearl, THIS JOURNAL, **67**, 1628 (1945); **68**, 429, 1100, 2180 (1946).

(4) Tiemann and Mendelsohn, *Ber.*, **10**, 59 (1877).

(5) Sabalitschka and Tietz, *Arch. Pharm.*, **269**, 545 (1931).

(6) Pearl and McCoy, *Food Industries*, **17**, 1458 (1945).

Experimental[7]

The data for the compounds prepared in this study are given in Table I. These were prepared by the following general methods.

Method I. Reaction of Vanillic Acid with Alcohol in Presence of Hydrogen Chloride.—The method is that described by Sabalitschka and Tietz.[5] **Method II. Reaction of Vanillic Alcohol in Presence of Sulfuric Acid.**

Method III. Reaction of Carbalkoxyvanilloyl Chloride with Alcohol or Phenol. Preparation of Phenyl Vanillate.—Carbethoxyvanilloyl chloride, prepared by the method of Heap and Robinson[8] from 24 g. (0.1 mole) of carbethoxyvanillic acid and excess thionyl chloride, was dissolved in 250 cc. of ether and treated with a solution of 10.4 g. (0.11 mole) of phenol in 100 ml. of *N* sodium hydroxide. The mixture was alternately cooled and shaken for one hour and then placed in the refrigerator overnight. The clear ether layer was separated, washed with water, and dried. The ether was removed below 30° under reduced pressure. The residue was cooled, stirred with 10% sodium carbonate solution, washed with water, dissolved in boiling acetone, and filtered. The cooled acetone filtrate was diluted with water. The solid which separated was recrystallized from petroleum ether to yield 18.8 g. of phenyl carbethoxyvanillate as white crystals melting at 63–64°.

Anal. Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.52; H, 5.18.

Hydrolysis of phenyl carbethoxyvanillate with *N* sodium hydroxide at room temperature gave a viscous oil which, when recrystallized from dilute methanol, yielded fine white needles of phenyl vanillate.

In similar manner was prepared guaiacyl carbethoxyvanillate which was obtained from petroleum ether as fine white needles melting at 93–94°.

Anal. Calcd. for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found: C, 62.17; H, 5.25.

Method IV. Reaction of Potassium Vanillate with Alkyl Chloride.—This is essentially the procedure described by Sabalitschka and Tietz[5] for the preparation of benzyl vanillate.

Method V. Reaction of Vanillic Acid with a Phenol in Presence of Phosphorus Oxychloride.—This method was patterned after that reported by Seifert[9] for the preparation of phenyl salicylate.

Toxicity toward Micro-organisms.—The testing technique employed in this study was that described by Appling and McCoy.[10] The test organisms were subjected separately to each of the esters, applied in concentrations ranging from 0.03 to 0.21% with 0.06% increments. If the inhibiting concentration was found to be lower than 0.03%, a range of concentrations from 0.003 to 0.03%, with increments of 0.006%, was tested. Thus, the inhibiting concentrations found in Table I are values which exceed the minimum by amounts depending upon the increments used in the testing procedure.

(7) All melting points given are uncorrected.

(8) Heap and Robinson, *J. Chem. Soc.*, 2336 (1926).

(9) Seifert, *J. prakt. Chem.*, [27] **31**, 472 (1885).

(10) Appling and McCoy, *Paper Trade J.*, **119**, no. 11, 116 (1944).

TABLE I

VANILLIC ACID ESTERS

Ester	Method of prepn.	Yield, %	B. p., °C.	Mm.	Solv.[a]	M. p., °C. (cor.)	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Inhibiting concentrations,[e] % *Bacillus mycoides*	Inhibiting concentrations,[e] % *Aspergillus niger*
Methyl[b]	I	97	118	2	A	63–64						0.21	0.21
	II	82											
Ethyl[b]	I	96	138	3	B	44						.15	.09
	II	92											
n-Propyl[b]	I	95	160	7	C	42–43						.09	.09
	II	85											
i-Propyl[b]	I	84			A	112–113						.09	.09
	II	80											
n-Butyl[b]	I	88	146–147	2	B	48–49						.015	.09
	II	89											
i-Butyl	II	88	125–126	2	B	56–57	$C_{12}H_{16}O_4$	64.27	64.24	7.19	7.07	.021	.03
s-Butyl	II	91	134	3	B	73–74	$C_{12}H_{16}O_4$	64.27	64.53	7.19	7.25	.09	.09
t-Butyl	III	60[c]			A	79–80	$C_{12}H_{16}O_4$	64.27	64.25	7.19	7.03	.09	.09
n-Amyl	I	91	165	4	B	35–36	$C_{13}H_{18}O_4$	65.53	65.38	7.61	7.49	.009	.15
i-Amyl	II	92	184	8	B	61–62	$C_{13}H_{18}O_4$	65.53	65.76	7.61	7.48	.009	.15
s-Butylcarbinyl	II	48	119–121	2			$C_{13}H_{18}O_4$	65.53	65.60	7.61	7.64	.03	.15
Diethylcarbinyl	II	23	112–114	2			$C_{13}H_{18}O_4$	65.53	65.62	7.61	7.63	.015	.09
n-Hexyl	II	59	129–130	2			$C_{14}H_{20}O_4$	66.64	66.36	7.99	7.97	.003	> .21
2-Ethylbutyl	I	78	166	1	A	37–38	$C_{14}H_{20}O_4$	66.64	66.37	7.99	7.92	.003	> .21
Benzyl[b]	IV	60	150–151	2	C	34–35						.015	.21
Phenyl	V	50[d]	185–186	3	D	93–94	$C_{14}H_{12}O_4$	68.84	68.75	4.95	5.03	.03	.15
Guaiacyl	V	10[f]	199–200	2	A	86–87	$C_{15}H_{14}O_5$	65.68	65.66	5.14	5.18	.03	> .21

[a] For recrystallization: A = petroleum ether (b. p. 65–110°); B = petroleum ether (b. p. 30–60°); C = dilute ethanol; D = dilute methanol. [b] This is a previously reported compound. See Sabalitschka and Tietz.[5] [c] 10% yield by Method IV. [d] 50% yield by Method III. [e] The inhibiting concentration against *Aerobacter aerogenes* was 0.21% in the case of *i*-butyl and *s*-butyl but was greater than this for every other ester in the table. [f] 60% yield by Method III.

Acknowledgment.—The authors are indebted to Virginia West Martin for the analyses reported in this paper.

Summary

A number of old and new esters of vanillic acid have been prepared. The inhibiting concentrations of these esters have been determined for three representative aerobic micro-organisms. Most of the esters effectively inhibited *Bacillus mycoides* and *Aspergillus niger* in low concentration.

APPLETON, WISCONSIN RECEIVED MAY 29, 1947

[CONTRIBUTION FROM THE DIVISION OF MEDICINAL CHEMISTRY, THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Substituted Sulfanilamidopyrimidines[1]

BY WILLIAM BRAKER, EDWARD J. PRIBYL, JOHN T. SHEEHAN, ERVIN R. SPITZMILLER AND W. A. LOTT

The success of the heterocyclic derivatives[2,3,4,5] of sulfanilamide as antibacterial agents, especially those of the pyrimidine type such as sulfadiazine, sulfamerazine and sulfamethazine, prompted the present investigation.

It was considered possible that by introducing various substituents such as alkoxy, alkoxyalkyl, β-alkoxyalkoxy, dialkoxymethyl or dialkylamino groups into one or more of the 4-, 5- and 6-positions of the pyrimidine moiety of the 2-sulfanilamidopyrimidine type, a chemotherapeutic agent more efficacious than the aforementioned might result. In particular it was hoped that a compound would be found possessing more desirable pharmacological properties with respect to absorption, persistence in the blood, degree of acetylation, tendency to combine with blood plasma and solubility of both the conjugated and unconjugated drug.

The synthesis of these compounds required the preparation of a variety of substituted acetoacetic

(1) Presented before the Division of Medicinal Chemistry of the American Chemical Society, Atlantic City, N. J., April 8–12, 1946.

(2) Ewins, Phillips and Newberry, British Patent 516,288.

(3) Lott and Bergeim, THIS JOURNAL, **61**, 3593 (1939).

(4) Roblin, Williams, Winnek and English, *ibid.*, **62**, 2002 (1940).

(5) Northey, *Chem. Rev.*, **27**, 85 (1940).