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Preparation of Vanillic Acid and Some of Its Metallic Salts

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PREPARATION OF VANILLIC ACID
AND
SOME OF ITS METALLIC SALTS

By
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PREFACE

Very little work has been done with vanillic acid and its derivatives since the time when the acid was first synthesized. There are usually good reasons why compounds showing such important properties as food preservatives have lain idle for over seventy-five years. It is of great interest to know the reasons behind this idleness and also to attempt to prepare some of the derivatives heretofore unreported.

This is the purpose for which this thesis has been written; that a little more knowledge will be contributed to a relatively virgin field. Submitted are the preparation of vanillic acid and some of its inorganic derivatives together with proposed uses of the derivatives. The uses will subsequently be tested and reported.

The author wishes to express her grateful appreciation to Mr. Herman Karl, Mr. Hamilton Pinkalla, Mr. Waldemar Rosenthal, and the American Bio-Synthetics Corporation for their help and advice without which interest in this field would not have been shown nor the problem attempted.

INTRODUCTION

For as long as people have known about vanilla beans, they have known about vanillin, the compound which characterizes the distinctive flavor of the bean. This knowledge, of course, did not include the specific structure or properties of the compound outside of odor and flavor, but, nevertheless, this definite something was recognized to be a part of the bean.

The first source of vanillin was from the vanilla bean which contains only two per cent vanillin formed on the surface of the bean as a fine white crystalline efflorescence. Such a low percentage makes the bean a poor commercial source. The first synthetically prepared vanillin was made by Tiemann in 1875 (26). He oxidized glucoside coniferin, which is found in the cambium of various coniferous woods, with aqueous chromic acid to get gluco-vanillin. Gluco-vanillin boiled with dilute mineral acids yielded glucose and vanillin.

$C_{16}H_{22}O_8 + 2H_2O = C_6H_3(O.CH_3)(O.C_6H_{11}O_5)(CHO)$
glucoside conferin   gluco-vanillin

$C_6H_3(O.CH_3)(O.C_6H_{11}O_5)(CHO) +$ dilute mineral acid
= glucose $+$ $3\text{-}(OCH_3),4\text{-}(OH)C_6H_3(CHO)$
vanillin

In 1876 Tiemann took out a patent for the oxidation of eugenol to vanillin (26). Almost simultaneously DeLaire took out a similar patent in France. Both discovered later that

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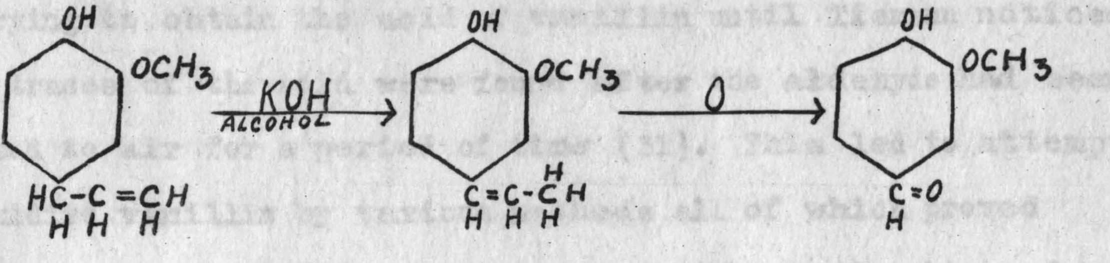
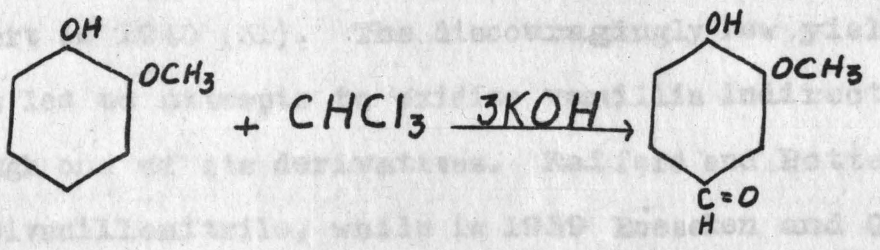
(26) Parry, E. J., *The Chemistry of Essential Oils and Artificial Perfumes*, *Vol. II*, London, Scott, Greenwood & Son, (1922) 198-9.

the yield of vanillin was greatly improved by converting eugenol to iso-eugenol before oxidation.



eugenol iso-eugenol vanillin

A little later guaiacol was tried as the starting material. One preparation used hydrocyanic acid in the presence of hydrochloric acid and zinc chloride. The vanillin was then extracted from an ether solution with sodium bi-sulfite. More classical is Tiemann and Reimer's condensation with chloroform in an alkaline medium (26). A mixture of vanillin and m-methoxy salicylic aldehyde resulted. The vanillin was then separated by steam.



guaiacol vanillin

Condensation with formic acid in the presence of phenylhydroxyamine sulphonate is also possible. Vanillin has been synthesized from m-amido-benzaldehyde, but this process is very cumbersome involving multiple diazotizations and hydrolyses, nitration, methylation, and reduction (26).

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(26) Parry, E. J., The Chemistry of Essential Oils and Artificial Perfumes, Vol. II, London, Scott, Greenwood & Son, (1922) 200-1.

Much more difficult than the synthesis of vanillin was its conversion to vanillic acid. Apparently no one thought of trying to obtain the acid of vanillin until Tiemann noticed that traces of the acid were found after the aldehyde had been exposed to air for a period of time (31). This led to attempts to oxidize vanillin by various methods all of which proved unsatisfactory. In 1905 Ciamician and Silber only obtained traces of the acid when they subjected vanillin to the action of sunlight in the presence of nitrobenzene (31). In 1919 Robbins and Lathrop obtained small amounts by allowing soil bacteria to act on vanillin (31). In 1931 Sabalitschka and Tietz fused vanillin with potash at 180-220°C. They obtained a mixture of protocatechuic and vanillic acids. The separation of the acids proved to be a long difficult process (52). Oxidation with ozone in ethyl acetate was carried out by Dorland and Hibbert in 1940 (31). The discouragingly low yields in all cases led to attempts to oxidize vanillin indirectly, i.e., through one of its derivatives. Raiford and Potter in 1933 used acetylvanillonitrile, while in 1939 Böeseken and Greup used acetylvanillin (3). The yields obtained were still too low to be of commercial value.

A great amount of work on this subject has been done by Dr. Irwin A. Pearl of the Institute of Paper Chemistry at Appleton, Wisconsin during the last seven years. It was found that considerable quantities of vanillin and vanillic acid were

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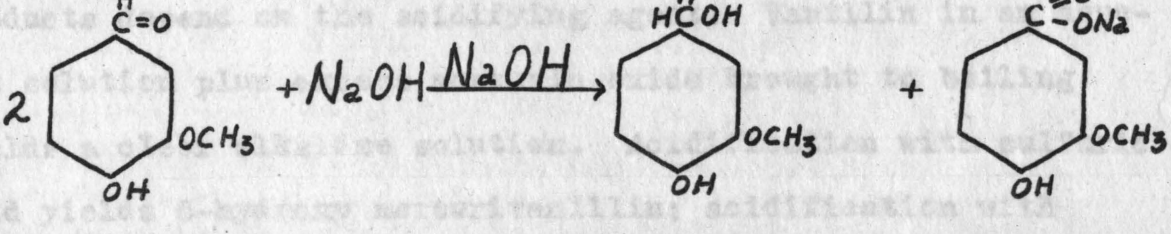
(31) Pearl, I. A., J. Am. Chem. Soc., 68, 429 (1946).

(52) Sabalitschka, T. and Tietz, H., Arch. Pharm., 269, 545 (1931).

(3) Böeseken, J. and Greup, J., Rec. trav. chim., 58, 528 (1939). (C. A. 33, 6273^5).

contained in the waste liquors of the paper and pulp mills and could be extracted quite readily with sodium bi-sulfite for vanillin and sodium bi-carbonate for the acid.

Back in 1931 Sabalitschka and Tietz had studied the effect of some vanillic acid esters on preventing fermentation of glucose by yeast (52). Studies of the esters of p-hydroxy benzoic acid showed their preservative power (24). These two pieces of information indicated that the esters of vanillic acid might exhibit preservative powers. Preservatives were very important at this time since the country was in the midst of World War II and the armed forces needed a means of keeping their large shipments of foods from spoiling. In order to prepare the esters it was necessary to have the acid. This again brought up the old problem of finding a method which would give satisfactory yields. Pearl proceeded through a catalyzed Cannizzaro reaction using silver oxide as the catalyst (30, 31). In alkaline medium with silver oxide, vanillin reacts to produce vanillic acid and vanillyl alcohol.



vanillin

vanillyl alcohol

sodium vanillate

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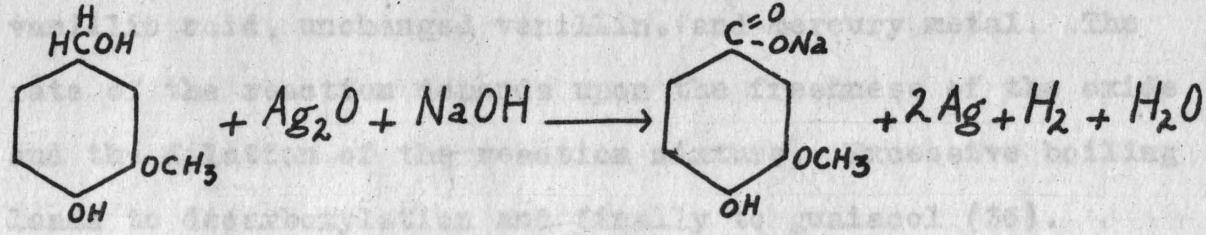
(52) Sabalitschka, T. and Tietz, H., Arch. Pharm., 269, 545 (1931).
(24) Neidig, C. P. and Burrell, H., Drug & Cosmetic Ind., 54, 408, 481 (1944).
(30) Pearl, I. A., J. Am. Chem. Soc., 67, 1628-9 (1945).
(31) Pearl, I. A., J. Am. Chem. Soc., 68, 429-32 (1946).



The silver metal thus produced can catalyze a similar reaction but without producing vanillyl alcohol as an intermediate. Schuerch reports that this catalytic oxidation is very sensitive to obscure differences in experimental conditions. He found Pearl's results impossible to duplicate (55). The use of similar oxides of mercury and gold show no Cannizzaro reaction (20, 29, 40). Further studies proved that the yield varies with the type and amount of silver used. Also the reaction must be allowed to proceed in alkaline medium (33). Through oxidation of basic-calcium lignosulfonate with silver oxide, Pearl was also able to obtain vanillic acid and vanillin (28).

Mercuric oxide reacts the some as silver oxide in regard to basic-calcium lignosulfonate, but in regard to vanillin the products depend on the acidifying agent. Vanillin in an aqueous solution plus excess mercuric oxide brought to boiling yields a clear alkaline solution. Acidification with sulfuric acid yields 5-hydroxy mercurivanillin; acidification with hydrochloric acid yields 5-hydroxy mercurivanillin and 5-hydroxy mercurivanillin; acidification with sulfur dioxide yields

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(55) Schuerch, C. Jr., J. Am. Chem. Soc., 70, 2293-4 (1948).
(20) Lewis, H. F. and Pearl, I. A., U. S. 2,433,227, Dec. 23, 1947.
(29) Pearl, I. A., U. S. 2,438,789, March 30, 1948.
(40) Pearl, I. A., U. S. 2,414,119, Jan. 14, 1947.
(33) Pearl, I. A., J. Org. Chem., 12, 79-84 (1947).
(28) Pearl, I. A., J. Am. Chem. Soc., 71, 2196-2200 (1949).

vanillic acid, unchanged vanillin, and mercury metal. The rate of the reaction depends upon the freshness of the oxide and the dilution of the reaction mixture. Excessive boiling leads to decarboxylation and finally to guaiacol (36).

Turning back to the original attempt of Sabalitschka and Tietz using a caustic fusion as the oxidation mechanism, Pearl ran a series of reactions using varying ratios of alkali to vanillin, different combinations of mixtures of sodium hydroxide and potassium hydroxide, and various maximum temperatures (27, 34). The reactions showed that using all sodium hydroxide produced no oxidation of vanillin while using all potassium hydroxide produced satisfactory results. The optimum yield resulted from using fifty per cent sodium hydroxide at a temperature of 206°C with a ratio of alkali to vanillin of two and one-half to one. As a general rule if the temperature is controlled around 200°C, the oxidation only proceeds as far as vanillic acid. However, if the temperature rises above 220°C for a long period of time or the heating time is excessively long, demethylation will take place and protocatechuic acid is formed. Vanillin and solutions of alkali at high temperatures give no reaction. Acidification with sulfur dioxide is preferable to mineral acids.

Combining the use of alkali and silver, Pearl found that if vanillin, sodium hydroxide, silver nitrate, and water were heated together and the resulting solution acidified with sulfur dioxide, only vanillic acid precipitates (32). But if

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(36) Pearl, I. A., J. Am. Chem. Soc., 70, 2008-10 (1948).

(27) Pearl, I. A. and Beyer, D. L., Ind. Eng. Chem., 42, 376-9 (1950).

(34) Pearl, I. A., J. Am. Chem. Soc., 68, 2180-1 (1946).

(32) Pearl, I. A., J. Am. Chem. Soc., 68, 1100-1, (1946).

hydrochloric acid is used for acidification, vanillic acid plus a little 5-nitro vanillic acid is formed.

Recently several indirect methods for the production of vanillic acid have been proposed. Challis and Clemo oxidized homovanillin with potassium permanganate in acetone but obtained only a twenty-five per cent yield (6). Much better yields were obtained by Misani and Bogert who oxidized acetylvanillin very slowly with potassium permanganate to acetylvanillic acid which was saponified (23). Although Fodor, Kiss, and Szerkerke were not trying to make vanillic acid, they did so by converting 3-methoxy-4-hydroxy propiophenone to the oximino ketone (10). With thionyl chloride the ketone undergoes a secondary Beckman rearrangement. The rearrangement product upon hydrolysis yields vanillic acid in the cold and vanilloyl-vanillic acid if heated.

The work done with the organic derivatives of vanillic acid is very limited. This is in part due to the fact that the means of obtaining the acid have been elusive. The ethyl ester was first prepared by Tiemann and Mendelsohn in 1877 (35). We do not get a glimpse of the potential power of the esters as preservative agents until 1931 when Sabalitschka and Tietz preformed their classical experiments. In addition to the ethyl ester, they prepared and experimented with the methyl, propyl, iso-propyl, and n-butyl esters.

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(6) Challis, A. A. L. and Clemo, G. R., J. Chem. Soc., 1692-7 (1947).

(23) Misani, F. and Bogert, M. T., J. Org. Chem., 10, 347 (1945).

(10) Fodor, G. et al., J. Org. Chem., 15, 227-32 (1950).

(35) Pearl, I. A. and McCoy, J. F., J. Am. Chem. Soc., 69, 3071-2 (1947).

Pearl again profited from these men and five years ago prepared and tested the properties of these known esters plus many more. The new ones were the iso-butyl, sec-butyl, tert-butyl, amyl, iso-amyl, 2-methyl butyl, 1-ethyl propyl, hexyl 2-ethyl butyl, phenyl esters of vanillic acid, o-vanillic acid, and 5-chlorovanillic acid (35, 37). The esters were prepared by one of five methods: 1. vanillic acid, alcohol, and hydrochloric acid; 2. vanillic acid, alcohol, and sulfuric acid; 3. carbalkoxyvanilloyl chloride and alcohol or the phenol; 4. potassium vanillate and alkyl chloride; 5. vanillic acid, the phenol, and phosphorus oxychloride.

Schuerch prepared vanillonitrile by treating vanillin with sulfuric acid and sodium azide. He found that by refluxing these same reactants he got a corresponding amount of vanillic acid (55). It is interesting to note that when both positions ortho to the hydroxyl group are substituted, it is impossible to oxidize the carbonyl group para to the hydroxyl group by ordinary means. Thus 5-halogen substitution products of vanillin cannot be oxidized to the corresponding acids. Raiford and his associates found that such compounds were converted to cinnamic acids by the Perkin reaction (48). The oxidation of the cinnamic acids yielded vanillin substitution products. In order to obtain the corresponding vanillic acid derivatives, they had to prepare the nitriles and oximes as intermediates.

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(35) Pearl, I. A. and McCoy, J. F., J. Am. Chem. Soc., 69, 3071-2 (1947).

(37) Pearl, I. A. and Beyer, D. L., J. Am. Chem. Soc., 71, 1066-8 (1949).

(55) Schuerch, C. Jr., J. Am. Chem. Soc., 70, 2293-4 (1948).

(48) Raiford, L. C. et al., Proc. Iowa Acad. Sci., 38, 171 (1931).

Heap and Robinson prepared benzoylvanillic acid, benzoyl vanilloyl chloride, and the anhydride of benzoyl vanillic acid (15). Benzoyl vanillic acid was prepared through vanillic acid and benzoyl chloride. Benzoyl vanillic acid plus phosphorous pentachloride yield benzoyl vanilloyl chloride. The anhydride forms when the chloride and the acid react in pyridine and dry ether. Twenty years later Rao and Seshadri set down definite reaction conditions for the same products (49).

Challis and Clemo have prepared a number of amines and amides of vanillic acid (7). They also prepared some sulfanilamides and their salts and tested the physiological possibilities of these compounds. Kubiczek and co-workers recently worked with the preparation of ortho alkylated derivatives of amides of vanillic acid, their p-nitrophenylhydrazones, and their oximes (19). Bruni and Levi prepared dithiovanillic acid together with its zinc and lead salts and the di-sulfide (4).

The metal salts of vanillic acid itself have gone almost unnoticed through the years. Tiemann reported the preparation of the sodium, potassium, ammonium, lead, and silver salts (58). He lists lead as the only insoluble salt. Silver vanillate decomposed when he attempted to recrystallize it. Vanino and Mussgnug prepared bismuth vanillate which is a hydrated compound holding two molecules of water (59). The preparation of

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(15) Heap, T. and Robinson, R., *J. Chem. Soc.*, 2336-44 (1926).
(49) Rao, K. V. and Seshadri, T. R., *J. Chem. Soc.*, 771-2 (1946).
(7) Challis, A. L. and Clemo, G. R., *J. Chem. Soc.*, 613 (1947).
(19) Kubiczek, G. *et al.*, *Monatsh.*, *77*, 52-7 (1947).
(4) Bruni, G. and Levi, T. G., Chem. Zentr. III, 1642 (1923).
(58) Tiemann, F., *Ber.*, *8*, 509-15 (1875).
(59) Vanino, L. and Mussgnug, F., *Arch. Pharm.*, *257*, 261-9 (1919).

bismuth salts is generally very difficult and expensive. One needs a pure form of the oxynitrate or hydroxide as the source of bismuth. But when bismuth nitrate is added to water a whole series of compounds can result depending upon the temperature of the water and the length of time that the solution is allowed to stand. At no one time is the precipitate a pure substance; there is co-precipitation at every step (47). After obtaining the pure inorganic bismuth compound, it is quite simple to react it with the organic acid or its sodium salt. Just heating the organic acid and bismuth nitrate in a little water causes a reaction and the organic bismuth salt separates on cooling (1). The reaction with the sodium salt is done in glycerol with bismuth nitrate and takes from two to eight days for completion (12). Salicylic acid reactions closely parallel similar vanillic acid reactions. Basic zinc salicylate has been prepared simply by agitating the acid, zinc oxide, and water (17). It might be supposed that vanillic acid would react similarly. Osakeyhtiö has patented a general formula for preparing alkali salts of organic acids. "A solution or suspension of a phenol or organic acid in a water insoluble medium, which is not a solvent for the corresponding alkali salts, is mixed with an aqueous solution of alkali hydroxide or carbonate and the medium is removed by distillation." (25).

Recently, some attention has been focused on phenyl metallic salts. Pfeiffer and Jäger reported the preparation

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(47) Prideaux, E. B. R. and Hewis, H. W., <u>J</u>. <u>Soc</u>. <u>Chem</u>. <u>Ind</u>., <u>41</u>, 167-71 (1922).
(1) Alcazar, A. and Casariego, C. S. F., <u>Bol</u>. <u>farm</u>. <u>militar</u>, <u>14</u>, 97-107 (1936).
(12) Godfrin, P., <u>J</u>. <u>pharm</u>. <u>chim</u>., <u>6</u>, 49-62 (1927).
(17) Kebrich, L. M., U. S. 2,501,127, March 21, 1950.
(25) Osakeyhtiö, K., Norw. 75,717, Oct. 10, 1949.

of phenyl mercuric salts of benzoic acid, m- and p-hydroxy benzoic acids, and salicylic acid (46). The active mercury compound is phenyl mercuric hydroxide made from phenyl mercuric acetate and potassium hydroxide in methyl alcohol. Dioxane is the reaction medium for the aromatic salts.

Research and experimentation with compounds which have no commercial value soon die out. It often happens that science has a need for a compound with particular properties but has difficulty finding that suitable compound. In the case of vanillic acid derivatives, the problem was not finding the suitable compound but finding an economical source of vanillic acid.

Vanillic acid itself acts as a plant growth promoter (14). This property may be connected with the power of the acid to inhibit bacterial growth and thus allow ordinary plant growth. Vanillic acid also acts as a cholagog agent and has cryptotoxic powers (5, 22, 60).

By far the greatest number of uses has been established for vanillic acid esters. Sodium benzoate has been used for some time in the United States as a food preservative. The effectiveness of benzoates increases with substitution in the para position. Work among the derivatives of vanillic acid was prompted by work done with the p-hydroxy benzoic acid esters (24). Germany has been using p-hydroxy benzoates for

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(46) Pfeiffer, P. and Jäger, H., Chem. Ber., 80, 1-6 (1947).
(14) Grace, H. H., Can. J. Research, 16, C, No. 3, 143-4 (1938).
(5) Chabrol, E. et al., Compt. rend. soc. biol., 107, 1240-3 (1931).
(22) Maximin, M. and Bocquentin, A., Physiol. Abstracts, 15, 168-9 (1930).
(60) Velluz, L., Compt. rend. soc. biol., 109, 269-71 (1932).
(24) Neidig, C. P. and Burrell, H., Drug & Cosmetic Ind., 54, 408, 481 (1944).

over twenty years as preservatives. The establishment of the Wiley Food and Drug Act of 1906 curtailed the use of chemical preservatives and stabilizers. Other preservative and sanitation measures took their place. The second World War led to a demand for chemical stabilizers and their use was allowed in very low concentrations. Among the organic preservatives which are now recognized are benzoates, salicylates, and esters of p-hydroxy benzoic acid. Among the bacteriostatic, fungistatic, and germicidal agents are salicylic acid, benzoic acid, and the sodium and ammonium salts of benzoic acid. A very important fact in connection with these particular powers in the case of benzoic and salicylic acid is that the compound is only effective in undissociated form (16). Vanillic acid esters which are similar in structure to p-hydroxy benzoates have a marked preservative action which is due to their ability to inhibit although not to destroy the growth of microorganisms. As mentioned before the first experiments with them showed that they prevented fermentation of glucose by yeast (52). In general the inhibiting power increases with an increase in molecular weight until reaching a maximum effectiveness with the butyl ester. The higher esters only deviate slightly from the maximum (16).

Pearl has had all the esters that he has prepared tested for their inhibiting power on the growth of molds, spore-forming bacteria, non-spore-forming bacteria, and heat resistant bacteria. Most of the esters inhibit the molds and the

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(16) Jacobs, B., Synthetic Food Adjuncts, New York, D. Van Nostrand Co., (1947) 223-9.

(52) Sabalitschka, T. and Tietz, H., Arch. Pharm., 269, 545 (1931).

spore-forming bacteria in low concentrations except the 5-chloro vanillates. In this case only the methyl and ethyl esters are effective. The iso- and sec-butyl esters of vanillic acid, the chlorohydrin esters, and the o-vanillates (to a lesser extent than the others) are the only successful ones against non-spore-forming bacteria (35, 37, 43).

The esters of vanillic acid have been tested and proved as preservatives in bread, cheese spreads, fruit and vegetable juices, milk, salted fish, and pickled herring. The method of preparing an ester for use is to first convert it to the sodium salt. This salt is then mixed with melted sterile Bacto nutrient agar to render it acid and thus liberate the free ester form (43). Under a pH of 9-10 esters exist free in alkaline solution. The butyl ester has a distinctive, unpleasant taste in concentrations starting with .15% which makes it unsuitable for human consumption (9). The ethyl ester has thus far proven to be the most useful because of its lack of taste and its greater solubility in water. Toxicity studies by the Kettering Laboratory of Applied Physiology of the University of Cincinnati Medical School show it to be less toxic in an aqueous medium than a corresponding amount of sodium benzoate.

A study of the ultraviolet absorption of vanillic acid and its esters showed that the esters generally filtered out all waves less than 3100A (38, 42). This led to the proposition

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(35) Pearl, I. A. and McCoy, J. F., J. Am. Chem. Soc., 69, 3071-2 (1947).

(37) Pearl, I. A. and Beyer, D. L., J. Am. Chem. Soc., 71, 1066-8 (1949).

(43) Pearl, I. A. and McCoy, J. F., Food Industries, 17,

(9) Evans, F. R. and Curran, H. R., Food Research, 13, 66-9 (1948).

(38) Pearl, I. A., J. Am. Chem. Soc., 71, 2331-3 (1949).

(42) Pearl, I. A., Am. Perfumer Essent. Oil Rev., 56, 25-8 (1950).

that the esters might be incorporated into cosmetics and suntan preparations. The burning of skin is caused by radiations of 2900-3200A, particularly 2967A. Further possible uses would be in transparent sheets or film as protectors and as plasticizers for products subject to embrittlement. Just recently, in fact, Pearl has patented a process whereby ethyl vanillate is impregnated in cellophane, cellulose, or paper base to prevent ultraviolet radiation (44).

Amino derivatives have found use in indoaniline dyes (61). Some exhibit definite analgesic properties (13). Sulphanilvanillylamide has been shown to have a slight antimalarial activity in chicks, but tests with other various sulfanilamides and amides against tuberculosis have been unsuccessful (7).

Vanillyl alcohol, vanillin, and syringic acid are used as stabilizers for ethyl cellulose plastic compositions and the possibility exists that vanillic acid might function in a like capacity (18).

A mild disinfectant and slime control agent for fisheries and tanneries has been found in 5-hydroxy mercurivanillic acid (36).

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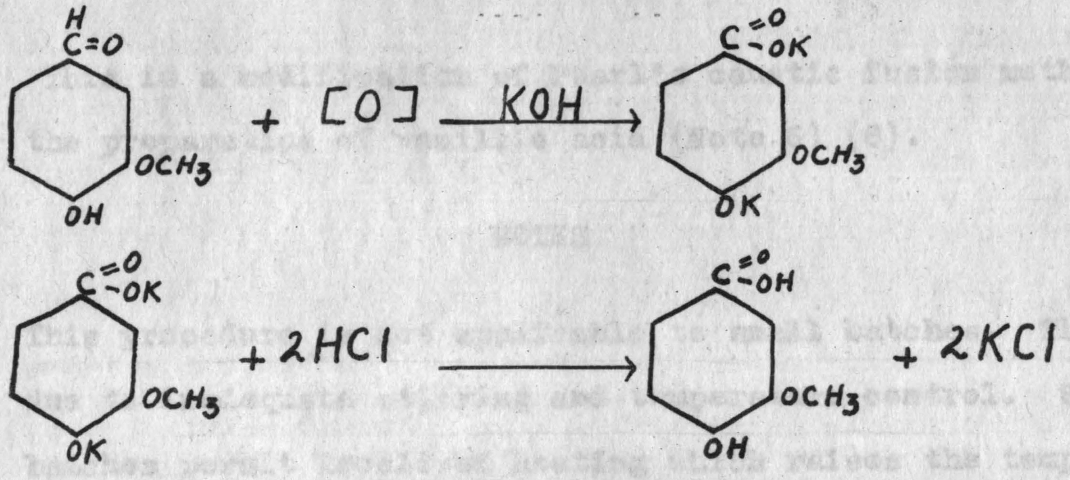
(44) Pearl, I. A., U. S. 2,568,760, Sept. 25, 1951.
(61) Vittum, P. W. and Brown, G. H., J. Am. Chem. Soc., 71, 2287-90 (1949).
(13) Goodson, L. H. and Moffett, R. B., U. S. 2,506,588, May 9,1950.
(7) Challis, A. A. L. and Clemo, G. R., J. Chem. Soc., 613-8 (1947).
(18) Koch, W. W., Brit. 577,875, June 4, 1946.
(36) Pearl, I. A., J. Am. Chem. Soc., 70, 2008-10 (1948).

EQUIPMENT AND APPARATUS

In the preparation of vanillic acid, the most important piece of apparatus is an efficient stirrer. A bread dough mixer was used as a stirring device. The mixer has a revolving wire stirrer which rotates around the sides of the reaction vessel. A thermocouple thermometer was wired onto the stirrer. The precipitated vanillic acid was spun off in a small spinner.

VANILLIC ACID



PROCEDURE (Note 1)

Dissolve 1,234g of 85% potassium hydroxide in 150cc of water, keeping the temperature at 125°C. With constant stirring, add 454g of vanillin at such a rate as to keep the temperature between 140°C and 150°C. After all the vanillin has been added, raise the temperature to 180°C and maintain it there until the oxidation is complete (Note 2). Test the reaction mixture with Fuchsin-aldehyde reagent (Note 3). A small amount of the reaction mixture dissolved in water and acidified gives the characteristic pink color with Fuchsin-aldehyde reagent in the presence of vanillin. After the reaction has cooled, dissolve it in six liters of water and acidify with concentrated hydrochloric acid (Note 4). Again cool the reaction and set aside for complete precipitation. Filter, wash free of acid, and recrystallize from hot water. The yield is 650g (Note 5). M.P. is 210-211°C.

METHOD OF PREPARATION

This is a modification of Pearl's caustic fusion method for the preparation of vanillic acid (Note 6) (8).

NOTES

1. This procedure is not applicable to small batches. This is due to inadequate stirring and temperature control. Small batches permit localized heating which raises the temperature and results in the production of protocatechuic acid.
2. The temperature must be maintained below 190°C because above this temperature demethylation takes place leading to the preparation of protocatechuic acid.
3. The Fuchsin-aldehyde reagent does not give conclusive results since the oxidation does not go to completion. The color test with ferric chloride for phenols fails in this case because the color given with vanillin is green, with vanillic acid is yellow, and with protocatechuic acid is blue. It is, therefore, impossible to discern one in the presence of another. Robbins and Lathrop started to work out quantitative color tests for mixtures of vanillin and vanillic acid (50). They used the reagent acid mercuric nitrate.
4. The reaction mixture must be carefully neutralized, since vanillic acid shows solubility in an excess of hydrochloric acid.

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(8) Cope, A. C., Ed., Organic Syntheses, Vol. 30, New York, John Wiley & Sons, Inc., (1950) 103-5.

(50) Robbins, W. J. and Lathrop, E. C., Soil Sci., 7, 475-85 (1919).

5. The yield of vanillic acid can be increased by extracting the filtrate with ether. The cost, danger, and inconvenience of using ether on a commercial scale is not compensated for by the gain in yield.
6. Pearl's method for caustic fusion was not followed because previous experience had shown that his reported results were impossible to obtain. This together with Schuerch's negative results when using silver oxide seems to indicate that Pearl has found some controlling factor which he does not wish to disclose and which permits him to obtain the results reported (55).

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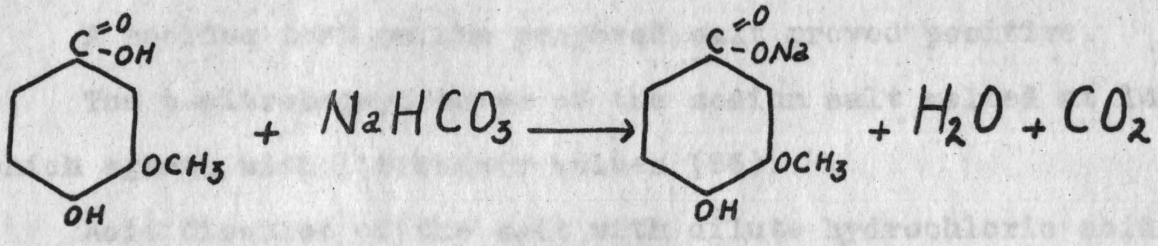
(55) Schuerch, C. Jr., J. Am. Chem. Soc., 70, 2293-4 (1948).

SODIUM VANILLATE



PROCEDURE

(a) To 250cc of methyl alcohol add 25g of vanillic acid and 13g of sodium bi-carbonate. Efficient stirring is maintained for 7.5 hrs. at 40°C. Filter and recrystallize from water. The yield is 20g.

(b) To 100cc of water alternately add 25g of vanillic acid and 13g of sodium bi-carbonate with constant stirring at room temperature. Reduce the volume of water by evaporation (Note 1). Allow to cool. Filter. Again reduce the volume of the filtrate, cool, and filter. Recrystallize from water. The yield is 23g.

NOTE

1. Heating the reaction mixture also serves to get rid of any excess bi-carbonate. For some reason the mother liquor becomes brown upon heating and discolors the crystals of sodium vanillate.

CONCLUSIONS THAT SODIUM VANILLATE HAD BEEN FORMED

A residue test on the proposed salt proved positive.

The p-nitrobenzyl ester of the sodium salt melted at 140°C which agrees with literature values (56).

Acidification of the salt with dilute hydrochloric acid precipitated vanillic acid which upon recrystallization melted at 210-211°C.

Charring the salt with concentrated sulfuric acid gave an almost quantitative yield (Note 1) of sodium sulfate based on the supposition that only the salt of the carboxyl group had been formed.

NOTE

1. The discrepancy of .1182g actual to .1220g theoretical yield was attributed to possible impurities in the vanillate. There is no method of assay even for vanillic acid.

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(56) Shriner, R. L. and Fuson, R. C., The Systematic Identification of Organic Compounds, Third Edition, New York, John Wiley & Sons, Inc., (1948) 225.

PREPARATION OF SALTS FROM SODIUM VANILLATE

Dissolve 1g of sodium vanillate in a minimum amount of water. Dissolve the theoretical amount of the particular inorganic salt in a minimum volume of water. Mix the two aqueous solutions and heat to boiling (Notes 1 & 2). Filter the hot solution.

NOTES

1. Silver vanillate cannot be heated since it decomposes with heat. In a solution containing sodium ions, the salt also decomposes. The decomposition is attributed to the sodium ion since exclusion of light has no effect in stopping the deposition of metallic silver. Further, Pearl reports a similar reaction occurring when he worked with silver catalyzed reactions (32). He was unable to explain why the sodium ion seems to act as a reducing agent in a solution of silver, sodium, and nitrate ions to form metallic silver and nitrite ions.
2. Originally all the salts had been filtered from a solution at room temperature. Work done with the lead salt seemed to indicate the inadvisability of this procedure. The yield of lead vanillate was ninety-eight per cent of the theoretical value, but in converting the vanillate to the sulfate the results showed .0906g of lead sulfate against the theoretical value of .1056g. This was interpreted as a possible contamination of the lead vanillate with other

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(32) Pearl, I. A., _J_. _Am_. _Chem_. _Soc_., 68, 1100-1 (1946).

salts. The hot solution was proposed to get rid of any co-precipitated sodium sulfate, lead sulfate, and sodium vanillate.

CONCLUSIONS THAT THE SALTS HAD BEEN FORMED

The salt taken up in a little water and acidified with concentrated hydrochloric acid (Note 1) goes into solution when heated. Vanillic acid crystals separate on cooling. These can be recrystallized for a melting point determination.

The filtrate, evaporated down, just neutralized with ammonium hydroxide precipitates the characteristic hydroxide. The precipitate is determined to be inorganic by a residue test (Note 2).

NOTES

1. Lead vanillate is acidified with concentrated sulfuric acid.
2. This analysis is only usable when there is a possibility of only a single metal being present.

EXPERIMENTAL DATA

PREPARATION OF SALTS

Inorganic Salt	Wgt. Taken for 1g of (1) $C_8H_8O_4$ (2) $NaC_8H_7O_4$	Cc of Reaction Medium	Yield Per cent	M. P. of Vanillic Acid
$AgNO_3$	.89g (2)	10 water	Not obtainable	210-211°C
$Ca(NO_3)_2 \cdot 5H_2O$	.67 (2)	10 water	61	209-210
$CuSO_4 \cdot 5H_2O$	.66 (2)	10 water	88	209-210
$KHCO_3$	.58 (1)	5 water	70	210-211
$NaHCO_3$	.50 (1)	10 CH_3OH	60	210-211
$NaHCO_3$	.50 (1)	5 water	65	210-211
$Pb(NO_3)_2$	.87 (2)	10 water	98	210-211
$Zn(NO_3)_2$	.78 (2)	10 water	75	209-210

SOME PROPERTIES OF THE SALTS

Salt	Color	Crystalline Structure
Ag vanillate	White	Gelatinous
Ca vanillate	White	Granular appearance*
Cu vanillate	Green	Solid mass*
K vanillate	White	Cubical
Na vanillate	White	Long needles
Pb vanillate	Very light gray	Short needles
Zn vanillate	Very light gray	Granular appearance*

*Crystalline structure is undeterminable by microscope.

SOME SOLUBILITIES* OF THE SALTS

Salt	H_2O 20°C	H_2O Hot	EtOH 20°C	EtOH Hot	Acetone 20°C	Acetone Hot
Ca vanillate	+	++	-	-	-	-
Cu vanillate	+	+	+	+	+	+
K vanillate	++	+++	-	-	-	-
Na vanillate	+++	+++	-	-	+	+
Pb vanillate	-	-	-	-	-	-
Zn vanillate	+	++	-	-	-	-

Salt	Ether 20°C	Ether Hot	Conc. HCl 20°C	Conc. HCl Hot	Conc. NH_4OH 20°C
Ca vanillate	-	-	-	+++	+++
Cu vanillate	+	++	-	+++	+++
K vanillate	-	-	-	+++	+++
Na vanillate	+	+	-	+++	+++
Pb vanillate	-	-	-	+	++
Zn vanillate	-	-	-	+++	+++

Symbol	Meaning
-	insoluble
+	very slightly soluble
++	slightly soluble
+++	soluble

*Solubility of .2g of the salt in 10cc of reagent.

DISCUSSION

The preparation of vanillic acid still needs work. Some definite means must be found whereby the stages of the reaction can be tested. This may come from a study of the kinetics of the reaction or from quantitative tests for vanillin and vanillic acid which can be made rapidly. The yield by this method is unsatisfactory. It may be that extraction with some other solvent which is cheaper and more easily handled would be the answer. This preparation on a laboratory scale, as mentioned, proceeds rapidly to protocatechuic acid. The temperature suddenly rises rapidly after remaining constant at 160°C. The heat of the reaction of the formation of vanillic acid which accounts for the temperature rise cannot be controlled without ruining the preparation. When the reaction begins to char, protocatechuic acid is being formed. The heat of this reaction plus the simultaneous reaction heat of vanillic acid keep the temperature too high for vanillic acid production. The larger the reaction mixture; the more slowly do the reaction heats cause a rise in temperature. Consequently, the process can be controlled.

As the inorganic salts of benzoic, salicylic, and gentisic acids come more and more into use, the need for a competent method of preparation becomes imminent. It would be thought that the reactions ould proceed to quantitative conversions under some specific conditions. The contamination of the inorganic products of the decomposition tend to rule out the possibility of running the reactions in organic media. There are, however, inorganic compounds which are soluble in organic solvents which might be usable. The soluble inorganic compounds would, of course, have to be the reaction products.

The means of preparation given in this paper have proved unsatisfactory for silver vanillate which decomposes in the reaction medium. Neither the magnesium nor the ferrous salt can be prepared by metathesis from the sodium salt in the molar ratios used.

SUMMARY AND CONCLUSIONS

A satisfactory method of preparing vanillic acid from vanillin has been sought for over seventy-five years. The answer as yet has not been found. The furthest advances toward the solution of the problem have been made by Pearl through the oxidation of vanillin in the presence of several oxides and by caustic fusion.

Although the organic derivatives of vanillic acid have received increased attention during the last few years, the inorganic salts have remained undeveloped. The extremely valuable properties exhibited by the known derivatives of vanillic acid and compounds similar in structure to vanillic acid led to the investigation of preparations of inorganic salts which might exhibit some of these same characteristics. Some of the metallic salts were prepared and tested for their properties. Correlation of structure and properties of similar compounds led to proposals of uses to which the salts might be applied.

Proposed Uses For Some of the Metallic Vanillates

Calcium vanillate

A calcium carrier to be put in foods.

A food preservative.

Copper vanillate

A fungicidal paint pigment.

A slime control agent and a mill disinfectant.

Lead vanillate

A stabilizer against light induced degradation of some plastics.

Silver vanillate

A photographic reagent.

Sodium vanillate

A food preservative.

An anti-oxidant.

Zinc vanillate

A reagent for improving the durability of paints.

SUGGESTIONS FOR FURTHER STUDY

Assay of vanillic acid.

Kinetics of the preparation of vanillic acid and its salts.

Preparation of vanillic acid anhydride.

Preparation of phenyl-metallic salts of vanillic acid.

Testing of biological and fungicidal properties of the vanillic acid salts.

Screening of the chemo-therapeutic properties of vanillic acid salts.

Study of the mechanics of the formation of the metallic salts from the acid.

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