[Contribution from The Institute of Paper Chemistry]

Reactions of Vanillin and its Derived Compounds. XXIII.[1] The Synthesis of 4,4'-Dihydroxy-3,3'-dimethoxybenzophenone[2,3]

By Irwin A. Pearl

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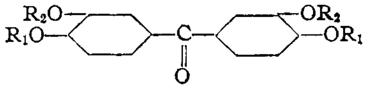
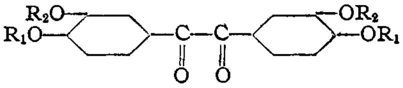
Vanillovanillone (4,4'-dihydroxy-3,3'-dimethoxybenzophenone) was synthesized from vanillil *via* the benzilic acid rearrangement of the bis-benzyl ether of vanillil and oxidative decarboxylation of the bis-benzyl ether of vanillilic acid thus obtained. The bis-benzyl ether of vanillovanillone was debenzylated to the desired vanillovanillone which was found to be identical with the product isolated from the oxidation of lignosulfonates or vanillil with cupric oxide and alkali. The lactide and isocoumaranone, formed by dehydration of the bis-benzyl ether of vanillilic acid, were also obtained.

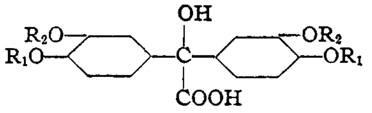
In a recent study on the oxidation of lignosulfonates with alkali and cupric oxide under pressure[4] the separation of a crystalline phenolic ketone melting at 155–156°, whose analysis corresponded with that for vanillovanillone (4,4'-dihydroxy-3,3'-dimethoxybenzophenone) (I), was reported. More recently, the same product was obtained by treatment of vanillil (II) with alkali and cupric oxide under the same conditions.[5] The formation of I from II in this reaction was accounted for by assuming rearrangement of II by alkali to the intermediate vanillilic acid (III) and decarboxylation and oxidation of the latter to I. The present paper reports the synthesis of vanillovanillone and proof of structure of the product isolated from lignosulfonate and vanillil oxidations.



I, $R_1 = H, R_2 = CH_3$
IV, $R_1 = R_2 = H$
V, $R_1 = R_2 = CH_3$
IX, $R_1 = C_6H_5CH_2, R_2 = CH_3$
X, $R_1 = CH_3CO, R_2 = CH_3$



II, $R_1 = H, R_2 = CH_3$
VII, $R_1 = C_6H_5CH_2, R_2 = CH_3$



III, $R_1 = H, R_2 = CH_3$
VI, $R_1 = R_2 = CH_3$
VIII, $R_1 = C_6H_5CH_2, R_2 = CH_3$

The first approach to the problem was an attempt to prepare vanillovanillone from vanillil *via* the intermediate vanillilic acid. However, every attempt to obtain a benzilic acid rearrangement of vanillil with alkali resulted in failure. Only the starting material was recovered. Even caustic fusion of vanillil at temperatures below 200° failed to cause rearrangement. More drastic fusion of vanillil with potassium and sodium hydroxides at 220°, in the presence of active silver, gave 3,3',4,4'-tetrahydroxybenzophenone (IV), which upon methylation with dimethyl sulfate and alkali gave 3,3',4,4'-tetramethoxybenzophenone (V), identical with the compound obtained on methylation of I from lignosulfonate and vanillil oxidations and with V reported by Ford-Moore,[6] who oxidized veratrilic acid (VI) with chromic and acetic acids.

Failure to obtain a benzilic acid rearrangement of vanillil led to a study of the benzilic acid rearrangement of the bis-benzyl ether of vanillil, 4,4'-dibenzyloxy-3,3'-dimethoxybenzil (VII). Reaction of VII with potassium hydroxide in butanol by a modification of the procedure of Ford-Moore[6] yielded the desired bis-benzyl ether of vanillilic acid (VIII). Oxidative decarboxylation of VIII with chromic acid in acetic acid gave the bis-benzyl ether of vanillovanillone (IX) which upon debenzylation with perchloric acid in acetic anhydride, according to Burton and Praill,[7] yielded the bis-acetate of vanillovanillone (X), identical with the bis-acetate of vanillovanillone obtained from lignosulfonate and vanillil oxidations.[4,5] Hydrolysis of X with ethanolic sodium hydroxide gave the desired vanillovanillone (I) identical in all respects with that isolated from lignosulfonate and vanillil oxidation mixtures.[4,5]

During the study of the conditions for obtaining the bis-benzyl ether of vanillilic acid by the reaction of the bis-benzyl ether of vanillil with potassium hydroxide in boiling butanol, several interesting compounds were isolated. The product of reaction, obtained in accordance with the reported Ford-Moore[6] procedure, upon recrystallization from benzene gave bluish crystals of the lactide, tetrakis-benzyl ether of vanillilide (XI). Upon treatment with chromic and acetic acids the lactide XI yielded the bis-benzyl ether of vanillovanillone (IX). In another similar experiment the reaction product was recrystallized first from benzene and then several times from acetic acid to yield the isocoumaranone, 2-hydroxy-4,4'-dibenzyloxy-3,3'-dimethoxydiphenylacetic acid lactone (XII). Debenzylation of XII with perchloric acid in acetic anhydride gave 2-hydroxy-4,4'-diacetoxy-3,3'-dimethoxydiphenylacetic acid lactone (XIII). The bis-benzyl ether of vanillovanillone could not be obtained from XII by the chromic acid oxidation

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[1] For paper XXII of this series, see This Journal, 75, 2630 (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] Presented before the Division of Organic Chemistry at the 125th Meeting of the American Chemical Society, Kansas City, Missouri, March 24 to April 1, 1954.

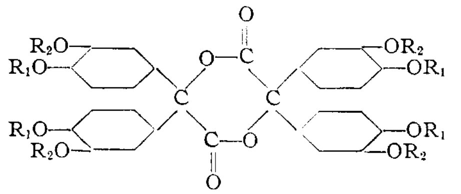
[4] I. A. Pearl and E. E. Dickey, This Journal, 74, 614 (1952).

[5] I. A. Pearl and D. L. Beyer, *ibid.*, 76, 2224 (1954).

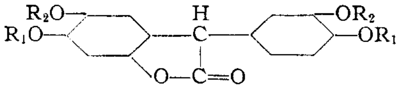
[6] A. H. Ford-Moore, *J. Chem. Soc.*, 952 (1947).

[7] H. Burton and P. F. G. Praill, *ibid.*, 522 (1951).

technique. Wasserman, Liu and Wasserman[8] recently reported an analogous pyrolysis of anisilic acid to yield first the bluish lactide, anisilide, which then rearranges to the isocoumaranone, *o*-hydroxy-*p*,*p*'-dimethoxydiphenylacetic acid lactone.



XI, $R_1 = C_6H_5CH_2$, $R_2 = CH_3$



XII, $R_1 = C_6H_5CH_2$, $R_2 = CH_3$
XIII, $R_1 = CH_3CO$, $R_2 = CH_3$

Experimental

All melting points are uncorrected.

3,3',4,4'-Tetrahydroxybenzophenone (IV).—A vigorously stirred mixture of 100 g. of sodium hydroxide, 100 g. of potassium hydroxide, 25 g. of metallic silver[9] and 30 cc. of water at 140° was treated with 14 g. of vanillil. The temperature was gradually raised to 220°, maintained there for 15 minutes and allowed to drop. When the temperature reached 120° the mixture was diluted with 300 cc. of water. The clear solution was acidified with concentrated hydrochloric acid and filtered. Upon cooling, the filtrate deposited granular crystals which were recrystallized from water in the presence of active carbon to give white crystals of hydrated IV melting at 230–231°. The product gave a bright green color with ferric chloride solution, and the ultraviolet absorption spectrum was almost identical with that of I, and showed the following maxima: λ_{max} 236 mμ, ϵ 16620; $\lambda_{shoulder}$ 280 mu, ϵ 10000; λ_{max} 323 mμ, ϵ 15420.

Anal. Calcd. for $C_{13}H_{14}O_7$: C, 55.32; H, 5.00. Found: C 55.69; H, 4.58.

A little IV was dissolved in 5% sodium hydroxide solution and warmed with an excess of dimethyl sulfate. The crystals which separated were filtered and washed with water. Recrystallized from ethanol, they melted at 145–146° and did not depress the melting points of mixtures with authentic 3,3',4,4'-tetramethoxybenzophenone[6] or with methylated I isolated from lignosulfonate or vanillil oxidations.[4,5] The ultraviolet absorption spectrum of V was almost identical with that of I.

4,4'-Dibenzyloxy-3,3'-dimethoxybenzil (VII).—A mixture of 60 g. (0.2 mole) of vanillil, 53 g. (0.42 mole) of benzyl chloride, 26.4 g. (0.4 mole) of 85% potassium hydroxide and 360 cc. of 95% ethanol was boiled under reflux for 5 hours. The mixture was diluted with water and basified with potassium hydroxide solution. The precipitate was filtered, washed with potassium hydroxide solution, then with water and dried to yield 88 g. of VII which was recrystallized from ethanol to give light yellow crystals melting at 141–142°.

Anal. Calcd. for $C_{30}H_{26}O_6$: C, 74.67; H, 5.43. Found: C, 74.73; H, 5.48.

VII was also prepared *via* the benzoin condensation. A solution of 300 g. of O-benzylvanillin in 400 cc. of ethanol was treated with a solution of 60 g. of potassium cyanide in 240 cc. of water, and the mixture was boiled 4 hours under reflux. An additional 60 g. of potassium cyanide was added, and the mixture boiled another 4 hours. The reaction mixture was poured into a large excess of cold water. The yellow taffy-like solid which separated was washed several times by decantation with cold water, dissolved in hot ethanol and treated with stirring with an excess of mixed Fehling solution. After boiling for one hour, the reaction mixture was poured into excess cold water, and the precipitate was washed several times with water by decantation and finally recrystallized from acetic acid to yield 160 g. of VII which melted at 141–142° and did not depress the melting point of a mixture with the authentic compound prepared above.[10]

4,4'-Dibenzyloxy-3,3'-dimethoxybenzilic Acid (VIII).—A boiling solution of 17 g. of potassium hydroxide in 90 cc. of butanol was treated with 25 g. of VII. After boiling for 10 minutes the mixture was cooled, diluted with water and distilled under reduced pressure until all butanol was gone. The aqueous mixture was cooled and acidified with dilute hydrochloric acid. The mixture was extracted with ether, which was dried and distilled to yield a heavy yellow oil. This oil was boiled with 100 cc. of benzene and filtered. The crystals which separated from the cooled benzene solution were filtered, washed with cold benzene, and then with a large volume of petroleum ether (b.p. 30–60°). The crystals of VIII weighed 18.6 g. and melted at 110–111° with gas evolution. The petroleum ether diluted filtrate yielded another 7 g. of white powder which upon recrystallizing from benzene yielded crystals of VIII, melting at 110–111°. The ultraviolet spectrum showed the following maxima: $\lambda_{shoulder}$ 232 mμ, ϵ 18700; λ_{max} 280 mμ, ϵ 6880.

Anal. Calcd. for $C_{30}H_{28}O_7$: C, 71.99; H, 5.64. Found: C, 71.86; H, 5.68.

4,4'-Dibenzyloxy-3,3'-dimethoxybenzophenone (IX).—A solution of VIII in warm glacial acetic acid was treated with chromic acid, according to Ford-Moore,[6] and the reaction mixture was diluted with water. The precipitate was washed with water by decantation and then recrystallized from ethanol to give colorless crystals of IX melting at 133–134°. The ultraviolet spectrum showed the following maxima: λ_{max} 236 mμ, ϵ 22600; $\lambda_{shoulder}$ 285 mμ, ϵ 13040; λ_{max} 318 mμ, ϵ 17700.

Anal. Calcd. for $C_{29}H_{26}O_5$: C, 76.63; H, 5.77. Found: C, 76.51; H, 5.83.

4,4'-Diacetoxy-3,3'-dimethoxybenzophenone (X).—The reaction of IX with acetic anhydride and a few drops of perchloric acid for 20 minutes, in accordance with the procedure of Burton and Praill,[7] yielded a product which, upon recrystallizing twice from ethanol in the presence of decolorizing carbon, yielded crystals of X melting at 148–149°, which did not depress the melting point of a mixture with the diacetate obtained from the cupric oxide oxidation of fermented sulfite waste liquor[4] or that from the oxidation of vanillil.[5] The ultraviolet spectrum showed the following maxima: λ_{max} 222 mμ, ϵ 26705; λ_{max} 265 mμ, ϵ 13630; λ_{max} 206 mu, ϵ 8150.

Anal. Calcd. for $C_{19}H_{18}O_7$: C, 63.68; H, 5.06. Found: C, 63.70; H, 5.12.

4,4'-Dihydroxy-3,3'-dimethoxybenzophenone (I).—Warming of X in excess 5% ethanolic sodium hydroxide and acidifying with dilute hydrochloric acid yielded a colorless oil which was extracted with ether. Removal of the ether gave a solid which was recrystallized from benzene to give crystals of I melting at 155–156°, which did not depress the melting points of mixtures with the analogous products obtained in the earlier oxidation studies.[4,5] The ultraviolet spectrum showed the following maxima: λ_{max} 233 mμ, ϵ 18210; $\lambda_{shoulder}$ 280 mμ, ϵ 10210; λ_{max} 320 mμ, ϵ 15910.

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.58; H, 5.15. Found: C, 65.74; H, 5.15.

Tetrakis-benzyl Ether of Vanillilide (XI).—The reaction mixture employed for the preparation of VIII, after boiling for 10 minutes, was cooled and treated with 500 cc. of water. The butanol layer was removed, and the aqueous solution was extracted with ether. The aqueous solution was acidified with dilute hydrochloric acid. The yellow precipitate was filtered, washed with water, air-dried and then boiled with benzene under a water-separatory head until no more water was collected. Upon cooling, the benzene solution deposited bluish crystals which were filtered and allowed to dry. The blue crystals turned white when completely dry

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[8] H. H. Wasserman, T. Liu and E. R. Wasserman, THIS JOURNAL, **75**, 2056 (1953).

[9] I. A. Pearl, *ibid.*, **68**, 429 (1946).

[10] In a similar benzoin condensation of O-benzylvanillin, S. F. Darling and R. Grishaber of Lawrence College extracted the reaction mixture with ether, dried the ether with sodium sulfate and allowed the ether solution to stand. A 35% yield of the intermediate 4,4'-dibenzyloxy-3,3'-dimethoxybenzoin was obtained in this manner as almost colorless crystals (from ethanol) melting at 111–112.5°. *Anal.* Calcd. for $C_{30}H_{28}O_6$: C, 74.38; H, 5.78. Found: C, 74.15; H, 5.42.

and melted at 139–140°. The ultraviolet spectrum showed a maximum at λ_{max} 282 mμ, ε 15820.

Anal. Calcd. for $C_{60}H_{52}O_{12}$: C, 74.67; H, 5.43. Found: C, 74.47; H, 5.52.

Reaction of XI with chromic acid in acetic acid, as described under IX, yielded IX. A mixed melting point of the two products was not depressed.

2-Hydroxy-4,4'-dibenzyloxy-3,3'-dimethoxydiphenylacetic Acid Lactone (XII).—A similar reaction mixture was diluted with 1000 cc. of water, acidified with sulfur dioxide, and extracted with ether. The ether was dried and distilled to yield 34 g. of viscous yellow tar. The tar was boiled with 75 cc. of benzene, filtered, and the filtrate was diluted with 600 cc. of petroleum ether (b.p. 65–110°). The precipitate was washed several times with petroleum ether by decantation and then warmed with 100 cc. of glacial acetic acid. A heavy precipitate separated from the clear solution upon warming. The mixture was cooled and filtered, and the precipitate was recrystallized from acetic acid to give colorless crystals of XII melting at 229–230°. The ultraviolet spectrum showed the following maxima: λ_{max} 218 mμ, ε 45700; λ_{max} 288 mμ, ε 15120; $\lambda_{shoulder}$ 324 mμ, ε 14700; λ_{max} 330 mμ, ε 15710.

Anal. Calcd. for $C_{30}H_{26}O_6$: C, 74.67; H, 5.43. Found: C, 74.48; H, 5.45.

Repeated attempts at oxidation of XII with chromic acid in acetic acid failed to yield IX.

2-Hydroxy-4,4'-diacetoxy-3,3'-dimethoxydiphenylacetic Acid Lactone (XIII).—A slurry of XII in acetic anhydride was treated with a few drops of perchloric acid as above to give a product which was recrystallized twice from methanol to give light yellow crystals of XIII melting at 234–235° with gas evolution. The ultraviolet spectrum showed the following maxima: λ_{max} 280 mμ, ε 23950; λ_{max} 317 mμ, ε 7600.

Anal. Calcd. for $C_{20}H_{18}O_8$: C, 62.17; H, 4.70. Found: C, 62.20; H, 4.68.

Ultraviolet Absorption Spectra.—Ultraviolet absorption spectra were determined in 95% ethanol with a Beckman model DU spectrophotometer. All concentrations were approximately 0.02 g. per liter.

Acknowledgment.—The author wishes to thank Mr. Harold Willemsen for the analyses and spectra reported in this paper.

APPLETON, WISCONSIN

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Benzothiophene Chemistry. VI. A Peroxide Effect in the Addition of Thiophenols to Benzothiophene 1-Dioxide

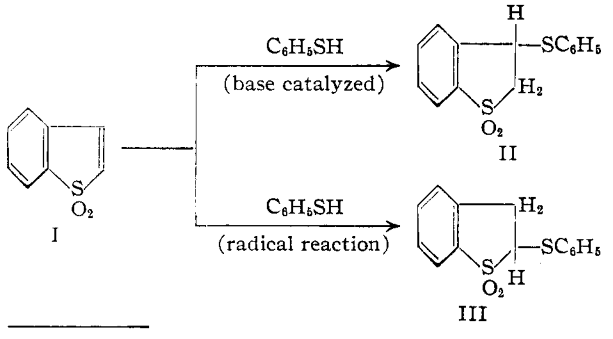
BY F. G. BORDWELL, R. D. CHAPMAN AND W. H. MCKELLIN

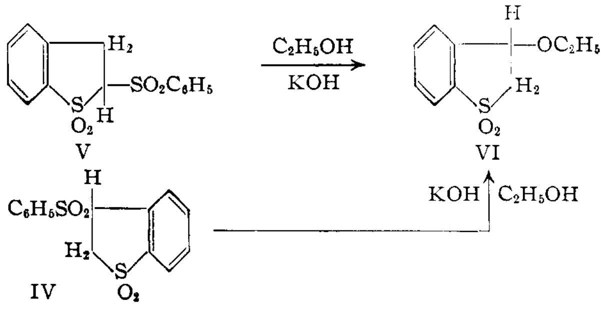
RECEIVED SEPTEMBER 25, 1953

In contrast to base-catalyzed addition of thiophenols to benzothiophene 1-dioxide, which occurred in the 3-position,[1] addition of arylthio radicals (ArS·) took place in the 2-position. Aliphatic thiols, however, gave 3-substituted products under all conditions. Also, thiophenol gave the same product with phenyl vinyl sulfone when the reaction was initiated thermally or by base catalysis.

In a previous paper in this series[1] it was demonstrated that the sulfonyl group in benzothiophene 1-dioxide (I) activated the α,β-double bond to addition of electron-donating reagents [amines, alcohols (basic catalyst), thiophenol (basic catalyst), etc.] in a manner comparable to the sulfonyl, carbonyl, cyano, etc., groups in similar open-chain molecules. It has now been found that the mode of addition of thiophenols to I is reversed in radical-type additions.

Thiophenol fails to add to I in alcohol solution in the absence of a basic catalyst, but when I was refluxed in thiophenol (b.p. 168°) solution for 30 minutes a high yield of addition product III isomeric with that II from the base-catalyzed reaction[1] was obtained. Oxidation of II to 3-phenylsulfonyl-2,3-dihydrobenzothiophene 1-dioxide (IV) was accomplished with 30% hydrogen peroxide in acetic acid. The structure of the disulfone, IV, follows from its preparation from 3-bromo-2,3-dihydrobenzothiophene 1-dioxide[1] and sodium benzenesulfinate in alcohol solution. The latter reaction is a direct displacement of bromide rather than elimination and addition, since sodium benzenesulfinate does not add to I under these conditions. Oxidation of III gave 2-phenylsulfonyl-2,3-dihydrobenzothiophene 1-dioxide (V). The isomeric pairs, II and III, and their oxidation products, IV and V, differed markedly in melting points, infrared spectra and other physical properties as did also comparable pairs prepared from I and *p*-thiocresol. Both IV and V reacted readily with alcoholic potassium hydroxide to give 3-ethoxy-2,3-dihydrobenzothiophene 1-dioxide (elimination of benzenesulfinic acid and addition of alcohol to I); IV appeared to react more readily than did V. These elimination reactions show that the phenylsulfonyl group is in each instance attached to the heterocyclic ring and completes the structure proof of V. The





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[1] F. G. Bordwell and W. H. McKellin, THIS JOURNAL, **72**, 1985 (1950).