[Contribution from the Laboratory of Organic Chemistry of the State University of Iowa]

EFFECT OF SUBSTITUENTS IN CERTAIN CONDENSATIONS OF BENZALDEHYDE

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Previous work in this Laboratory[1] has shown that the interaction of bromine and chlorine derivatives of vanillin with amino compounds is not noticeably hindered unless both positions ortho to the aldehyde group are substituted; even then the hindrance is much less than might be expected. For this reason it was desired to test these derivatives in other reactions involving the aldehyde radical. The benzoin condensation and the Claisen reaction suggested themselves.

The discovery of the benzoin condensation is credited to Wöhler and Liebig,[2] who obtained benzoin by treatment of bitter almond oil with potassium hydroxide solution.[3] Subsequent work has shown that certain substituents prevent this condensation from taking place. Thus, *o*- and *p*-nitrobenzaldehydes,[4] salicylaldehyde,[5] 5-bromo- and 5,6-dibromovanillin[6] failed to give the expected benzoins when treated with potassium cyanide in the usual way. One purpose of the present work was to test the effect of substituents indicated in the last two examples by further study of vanillin derivatives. The list of known benzoins is surprisingly small, and it may be supposed that the character of certain substituents in the required starting material is responsible.

Irvine[5] found that salicylaldehyde methyl ether undergoes the benzoin condensation if none of the free salicylaldehyde is present, which suggests that the hydroxide radical may prevent the reaction. This radical as a phenyl substituent causes acidic properties, and since Lachman[7] found

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[1] Raiford and others, This Journal, **49**, 1077, 1571 (1927); **50**, 2556 (1928); **52**, 4576 (1930).

[2] Wöhler and Liebig, *Ann.*, **3**, 254, 276 (1832).

[3] It has been shown [Stern, *Z. physik. Chem.*, **50**, 513 (1905)] that the benzoin condensation takes place only in the presence of alkali cyanides. But even under these conditions benzoic acid, benzyl alcohol and mandelic acid nitrile are formed in small amounts [Ekecrantz and Ahlqvist, *Centr.*, **79**, 1689 (1908); Lachman, This Journal, **46**, 723 (1924)]. The formation of benzoin in Wöhler and Liebig's experiments, in which they isolated also benzoic acid and an "oily body that is no longer bitter almond oil" and which was shown by Cannizzaro [*Ann.*, **88**, 129 (1853)] to be benzyl alcohol, was doubtless due to the presence of hydrocyanic acid in the bitter almond oil used by them.

[4] Homolka, *Ber.*, **17**, 1902 (1884).

[5] Irvine, *J. Chem. Soc.*, **79**, 670 (1901).

[6] Raiford and Hilman, This Journal, **49**, 1571 (1927).

[7] Lachman, *ibid.*, **46**, 708 (1924).

that acids prevent the condensation, it was interesting to study the behavior of the alkali salts of such compounds. When the potassium salts of 5-bromovanillin and *p*-hydroxybenzaldehyde, respectively, were subjected to the action of potassium cyanide in the usual way, the starting materials were recovered almost quantitatively, and no benzoin was detected. Vanillin, likewise, does not give a benzoin, but the methyl ether, veratraldehyde (see experimental part), gave a dark-colored oil that was shown to contain a large percentage of starting material, some of the required benzoin,[8] possibly in polymeric form, and a small quantity of 3,4-dimethoxybenzoic acid. The acid was identified by comparison with a sample synthesized in a different way and by a study of its methyl ester. The presence of the benzoin was indicated by the fact that a portion of the product was converted to the corresponding benzil in nearly quantitative yield by oxidation of its alkaline solution.

Halogenated derivatives were next studied. When 3,4-dimethoxy-5-bromobenzaldehyde was subjected to the action of potassium cyanide in the usual way, some starting material, a small quantity of the corresponding dimethoxybromobenzoic acid and a viscous resin-like material were obtained. This resin reduced Fehling's solution and was oxidized to the required benzil, which latter was obtained in crystalline form and identified by study by its hydrazone.[9] The resin must have contained some of the corresponding benzoin, possibly in polymeric form. When the 2-bromo- and 6-bromo-derivatives of 3,4-dimethoxybenzaldehyde were boiled with the cyanide solution, starting material alone was recovered although special search was made for the acid and the benzoin. In the case of the 6-derivative, which was most readily obtained in quantity, attempts to bring about the condensation by variation of the kind and amount of solvent used were unsuccessful. Methyl, ethyl, propyl, isopropyl and *sec.*-amyl alcohols, and pyridine were used as solvents in different experiments, and the time of heating was varied in repetitions of each. Nothing but starting material could be isolated from the reaction mixtures.

These failures, as well as observations made by others, tend to support the view of Staudinger[10] according to which only aldehydes that are

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[8] Hörbye [Dissertation, Dresden, 1917, p. 33] found that treatment of ethylvanillin with varying portions of potassium cyanide solution, with and without alcohol, at room temperature and heated on the water-bath, for short and long periods, gave only a trace of benzoin (for which the author offered no experimental identification), a small amount of resin, and some ethylvanillic acid, while the greater portion of the starting material remained unchanged. Likewise, methylvanillin failed to undergo the condensation.

[9] The fact that only one hydrazine residue was introduced, although an excess of reagent was employed, suggests steric hindrance.

[10] Staudinger, *Ber.*, **46**, 3535 (1913).

easily oxidized to the related acids may be expected to undergo the benzoin condensation.[11]

A second purpose in this work was to test these vanillin substitution products toward the Claisen[12] reaction, by which it was hoped to obtain unsymmetrical ketones for use in further study of the rearrangement of the hydrazones of α,β-unsaturated ketones to pyrazolines.[13] Both mono- and dibenzalacetone derivatives were obtained from 5- and 6-bromovanillin; 5-nitrovanillin gave only a monobenzal derivative. The monovanillal derivatives were obtained by treatment of the required aldehyde with a large excess of acetone with sodium hydroxide as condensing agent; to obtain the di-compounds the calculated amount of acetone was used with concentrated hydrochloric acid as condensing agent.[14]

Experimental Part

3,3′,4,4′-Tetramethoxybenzil.—A mixture of the required methylvanillin,[15] 15 cc. of alcohol, 10 cc. of water and 1 g. of potassium cyanide was boiled under reflux for half an hour, and poured into 50 cc. of cold water. The dark-colored oil that separated was removed by extraction with ether, the liquid dried over anhydrous sodium sulfate, the ether distilled and the residue fractionated under partial vacuum. At 160° and 20 mm. about 60% of the material passed over as an oil that solidified on standing. It melted at 42° and did not depress the melting point of methylvanillin. The viscous amber-colored residue solidified upon cooling to a brittle amorphous solid that was not obtained in crystalline form. It reduced Fehling's solution and was probably the required benzoin or a polymer.[16] When a portion of it was allowed to stand exposed to the air for several months it became opaque in appearance and seemed to lose its amorphous character. Crystallization of this product from acetic acid gave small, yellow, closely matted needles, m. p. 219–220°.[17] A second portion was con-

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[11] *o*- and *p*-hydroxybenzaldehyde [Dakin, *Am. Chem. J.*, **42**, 478 (1909)], vanillin [Tiemann, *Ber.*, **9**, 415 (1876)] and 5-bromo-vanillin [Brady and Dunn, *J. Chem. Soc.*, **107**, 1859 (1915)] cannot be oxidized to the respective acids by the usual means, and neither of them undergoes the benzoin condensation.

[12] Although Chiozza [*Ann.*, **97**, 350 (1856)] first studied this type of reaction, and Baeyer [*ibid.*, sp. **5**, 82 (1867)] referred to the action of dehydrating agents on a mixture of benzaldehyde and acetone, its development is due to Claisen and co-workers [*Ber.*, **14**, 349, 2468 (1881); *Ann.*, **223**, 138 (1884), and subsequent papers].

[13] Raiford and Davis [This Journal, **50**, 156 (1928)] found that in some instances this rearrangement occurs so rapidly that it is impossible to isolate the hydrazone. Subsequent work, soon to be published from this Laboratory, indicates that the direction of the rearrangement is influenced largely by substituents in the phenyl nuclei of the ketones.

[14] Done by a modification of the method used by Glaser and Tramer [*J. prakt. Chem.*, **116**, 331 (1927)]. This paper contains important references to similar work.

[15] Obtained in 89% yield by Perkin and Robinson's [*J. Chem. Soc.*, **91**, 1079 (1907)] method. See, also, modification by Decker and Koch [*Ber.*, **40**, 4794 (1907)].

[16] A product which probably had the composition of this one was obtained by Vanzetti [*Atti accad. Lincei*, **24**, 467 (1915)], who failed to secure a solid product or to note the presence of starting material and 3,4-dimethoxybenzoic acid.

[17] Fritsch [*Ann.*, **329**, 53 (1903)] recorded 219–220° for this benzil obtained by

verted almost quantitatively into the corresponding benzil when air was bubbled for an hour through a boiling alcoholic potash solution of it. The product was identified by analysis and molecular weight determination.[18]

Anal. Subs., 0.3230: CO_2, 0.7365; H_2O, 0.1565. Calcd. for $C_{18}H_{18}O_6$, C, 65.42; H, 5.49. Found, C, 65.00; H, 5.42. 0.0395g. of substance dissolved in 0.8687 g. of camphor, $\Delta = 5.8°$. Molecular weight $= (40{,}000)(0.0395)/(0.8687)(5.8) = 314$. Calcd. for $C_{18}H_{18}O_6$: mol. wt., 330. Found: 314.

The aqueous layer left after extraction of the oil indicated above was warmed to expel ether, acidified and allowed to stand. The solid that separated was readily soluble in alkali solution and reprecipitated by acids. Repeated crystallization from water gave colorless needles, m. p. 180°. A mixture of the product here in question and 3,4-dimethoxybenzoic acid, prepared as directed by Koelle,[19] melted without depression.

5-Bromo-3,4-dimethoxybenzaldehyde.—This was made by a variation of Dakin's[20] method. Fifty grams of 5-bromovanillin was dissolved in 300 cc. of methyl alcohol and 13 g. of potassium hydroxide dissolved in the smallest possible quantity of water was added. While the mixture was kept warm on a water-bath, 80 cc. of dimethyl sulfate was added as rapidly as the vigor of the reaction would permit, and the mixture was then evaporated almost to dryness. About 200 cc. of water was next added, the mixture extracted with ether, the extract dried over anhydrous sodium sulfate and the ether distilled off. The residue distilled between 157 and 162° at 5 mm.; yield 95%. The product melted at 59.5°, which is also the melting point of the first portion to solidify from the melted material.[21] The purity of the product here under consideration was checked by a Carius determination of halogen.

Anal. Subs., 0.2923: AgBr, 0.2243. Calcd. for $C_9H_9O_3Br$: Br, 32.65. Found: Br, 32.66.

5,5′-Dibromo-3,3′,4,4′-tetramethoxybenzil.—A mixture of 15 grams of 5-bromo-3,4-dimethoxybenzaldehyde in 100 cc. of alcohol and 2 g. of potassium cyanide in 10 cc. of water was refluxed for five hours, and then poured into five volumes of water. Extraction with ether removed a resinous material that reduced Fehling's solution, and was readily soluble in cold alcohol. The aqueous layer (A) was reserved for further examination. The resin was allowed to stand exposed to the air for several weeks, and the small yellow crystals that had separated were isolated by extracting the remaining resin with cold alcohol, in which the crystals were almost insoluble. Several repetitions of this treatment gave 4.5 g. of material which, after crystallization from

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the action of nitrous acid on tetramethoxyisonitrosodesoxybenzoin in accordance with the method described by Manasse [*Ber.*, **21,** 2176 (1888)].

[18] The method of observing the melting point required in the Rast method [*Ber.*, **55,** 3727 (1922)] was made more convenient and the accuracy of the determination improved by adoption of a suggestion of Dr. E. P. Clark [Bureau of Chemistry and Soils, U. S. Department of Agriculture]. This involved the replacement of the ordinary magnifying lens by a binocular magnifier.

[19] Koelle's [*Ann.*, **159,** 241 (1871)] product melted at 170–171°, and was probably impure.

[20] Dakin, *Am. Chem. J.*, **42,** 494 (1909).

[21] Dakin reported 65–66°. He recorded no analysis for his product, but assumed that its purity was confirmed by the fact that it could be oxidized into the corresponding acid, the melting point of which he did not check, and that the methyl ester of this acid melted at 69–70°, although Zincke and Francke [*Ann.*, **293,** 185 (1896)] found 71–72° for the ester.

acetic acid, was obtained in yellow needles[22] that melted at 209–210°. It did not reduce Fehling's solution. Analysis for bromine and molecular weight determination indicated the benzil.

Anal. Subs., 0.2037: AgBr, 0.1585. Calcd. for $C_{18}H_{16}O_6Br_2$: Br, 32.78. Found: Br, 33.11. 0.0277 g. of substance dissolved in 0.4443 g. of camphor, $\Delta = 5.0°$. Molecular weight $= (40{,}000)(0.0277)/(0.4443)(5.0) = 498.7$. Calcd. for $C_{18}H_{16}O_6Br_2$: mol. wt., 488. Found: 498.7.

Mono-*p*-bromophenylhydrazone of 5,5′-Dibromo-3,3′,4,4′-tetramethoxybenzil.—To a glacial acetic acid solution of 2 g. of the required benzil slightly more than two molecular proportions of *p*-bromophenylhydrazine was added, the mixture gently warmed for a few minutes and then allowed to stand for twenty-four hours. Recrystallization of the solid product from acetic acid gave yellow needles; m. p. 155–156°. The yield of purified material was 37%.

Anal. Subs., 0.1280: AgBr, 0.1115. Calcd. for $C_{24}H_{21}O_5N_2Br_3$: Br, 36.53. Found: Br, 37.07.

5-Bromo-3,4-dimethoxybenzoic Acid.—The aqueous layer (A) left when the ether layer was separated after extraction of the mixture in which an attempt was made to prepare 5,5′-dibromo-3,3′,4,4′-tetramethoxybenzoin, was warmed to remove dissolved ether, acidified and allowed to stand. The solid deposited, about 2 g., was recrystallized from water. It was acidic in character, melted at 190°, and was regarded as 5-bromo-3,4-dimethoxybenzoic acid. Zincke and Francke[23] reported 191° for this product, prepared by a different method, but did not determine its bromine content.

Anal. Subs., 0.2605: AgBr, 0.1883. Calcd. for $C_9H_9O_4Br$: Br, 30.65. Found: Br, 30.76.

2-Bromo-3,4-dimethoxybenzaldehyde.—This was obtained in 74% yield by alkylation of 2-bromovanillin[24] as described above under the 5-bromo compound. After two crystallizations from dilute methyl alcohol it was obtained in colorless needles that melted at 85–85.5°.

Anal. Subs., 0.2310: AgBr, 0.1777. Calcd. for $C_9H_9O_3Br$: Br, 32.65. Found: Br, 32.74.

Di-(5-bromovanillal)-acetone.—To a suspension of 15 g. of 5-bromovanillin in a mixture of 150 cc. each of glacial acetic and concentrated hydrochloric acid 2.3 cc. of acetone was added, and the mixture allowed to stand with occasional shaking for four weeks.[25] Gentle warming at the time of shaking seemed to aid in dissolving the solid and possibly favored the reaction. When the mixture was poured into a large volume of water a greenish yellow solid was precipitated; yield, 87%. The solid was shaken with dilute sodium hydroxide solution, the mixture filtered and the filtrate acidified with acetic acid. After several repetitions of this treatment the solid was heated with glacial acetic acid until nearly all had dissolved, the mixture filtered, the filtrate poured into several volumes of water, and the precipitate recrystallized from acetic acid. Bright yellow needles that melted at 230–231° were obtained.

Anal. Subs., 0.2295: AgBr, 0.1776. Calcd. for $C_{19}H_{16}O_5Br_2$: Br, 33.05. Found: Br, 32.93.

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[22] When the remaining resin from which this benzil had separated was exposed in an open vessel for several months, a nearly colorless sublimate appeared on the walls of the container. This material was identified as 5-bromo-3,4-dimethoxybenzaldehyde.

[23] Zincke and Francke, *Ann.*, **293**, 184 (1896).

[24] Raiford and Stoesser, THIS JOURNAL, **49**, 1077 (1927).

[25] A modification of Glaser and Tramer's [*J. prakt. Chem.*, **116**, 331 (1927)] method.

6-Bromovanillalacetone.—Fifteen grams of 6-bromovanillin[26] was dissolved in a mixture of 45 cc. of acetone, 33 cc. of 10% solution of sodium hydroxide and 90 cc. of water[27] and the liquid allowed to stand for several days, during which time a deep red color developed. When the intensity of color increased no further the mixture was poured into several volumes of water, acidified with acetic acid, and the yellow solid collected by filtration; yield, 92%. Two crystallizations from dilute acetic acid gave bright yellow needles; m. p., 153–154°.

Anal. Subs., 0.2496: AgBr, 0.1737. Calcd. for $C_{11}H_{11}O_3Br$: Br, 29.52. Found: Br, 29.62.

Di-(6-bromovanillal)-acetone.—This was obtained in 75% yield by the above described method for the 5-bromo compound. The product was purified by extraction of foreign material by boiling with glacial acid, in which the desired product was almost insoluble. A bright yellow powder that melted at 255–256° was secured.

Anal. Subs., 0.2363: AgBr, 0.1872. Calcd. for $C_{19}H_{16}O_5Br_2$: Br, 33.05. Found: Br, 32.94.

5-Nitrovanillalacetone.—Fifteen grams of 5-nitrovanillin[28] was mixed with acetone and dilute alkali solution, allowed to stand for ten days and worked up as specified under the 6-bromo derivative. Crystallization from water gave orange-colored needles; m. p. 156°.

Anal. Subs., 0.2171: CO_2, 0.4423; H_2O, 0.0932. Calcd. for $C_{11}H_{11}O_5N$: C, 55.69; H, 4.63. Found: C, 55.56; H, 4.80.

Summary and Conclusions

1. Several substituted benzaldehydes have been subjected to the action of potassium cyanide as required in the benzoin condensation. In cases where a bromine atom occupied the ortho position with respect to the aldehyde group, the required benzoin was not obtained.
2. Some confirmation has been found for the theory that the hydroxyl group as a substituent in benzaldehyde prevents the benzoin condensation.
3. Several new substituted benzalacetones have been prepared.
4. Further work is in progress in this Laboratory.

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[26] Raiford and Stoesser, THIS JOURNAL, **49**, 1077 (1927).

[27] Francesconi and Cusmano, *Gazz. chim. ital.*, [II] **38**, 70 (1908).

[28] Prepared as directly by Bentley [*Am. Chem. J.*, **24**, 171 (1900)].