Summary

1. The Jacobsen reaction on the bromotetramethylbenzenes consists in the migration of a bromine atom to give the corresponding dibromo compound and prehnitene sulfonic acid. The usual by-products of sulfur dioxide and a brown amorphous material are obtained.

2. The first step in the reaction is sulfonation, and the sulfonic acid is the rearranging molecule.

3. Whether the reaction consists of the rearrangement or merely hydrolysis of the sulfonic acid, depends on the temperature. At very low and very high temperatures, the main reaction is hydrolysis. The best temperature for the rearrangement is from 25 to 65°.

4. The dibromo compounds cannot be identified by their mixed melting points, as the depressions are only about 2°, but the dinitro compounds give depressions of 15° or more and the series dibromo compound, hydrocarbon, dinitro compound can be used as a method of identification.

5. The dibromo compounds do not rearrange in contact with sulfuric acid.

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Preparation of Substituted Vanillic Acids

BY L. CHAS. RAIFORD AND DWIGHT J. POTTER

Benzaldehyde[1] and anisaldehyde[2] are easily oxidized by air to the corresponding acids. *p*-Hydroxybenzaldehyde[3] and protocatechuic aldehyde[4] are more resistant and are not oxidized readily by potassium permanganate solution but require fusion with caustic potash to give the acids. Tiemann[5] found that treatment of vanillin solutions with oxidizing agents caused hardly any change, or else complete decomposition, depending on conditions. Vogel[6] prepared 5-nitrovanillic acid, and Brady and Dunn[7] obtained the 5-bromo compound by hydrolysis with alkali of the corresponding nitriles which, in turn, had been obtained from the respective oximes. Bromovanillin could not be oxidized by acetic acid solution of chromic acid or by alkaline permanganate.

The recent syntheses in this Laboratory of all chlorine and bromine

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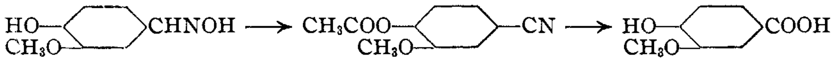
(1) Wöhler and Liebig, *Ann.*, **3**, 250 (1832).
(2) Cahours, *ibid.*, **56**, 308 (1845).
(3) Bücking, *Ber.*, **9**, 529 (1876).
(4) Fittig and Remsen, *Ann.*, **159**, 150 (1871).
(5) Tiemann, *Ber.*, **9**, 415 (1876).
(6) Vogel, *Monatsh.*, **20**, 389 (1899).
(7) Brady and Dunn, *J. Chem. Soc.*, **107**, 1860 (1915).

substitution products of vanillin required by theory provided material from which the corresponding acids might be prepared. Since the latter cannot be obtained by oxidation of the aldehydes in the usual ways the methods of Vogel and of Brady and Dunn were tested further. The oximes, prepared as directed in the literature,[8] were converted by boiling with acetic anhydride into the acetoxynitriles, and the latter were hydrolyzed by solution of potassium hydroxide, as indicated below.



In general, good yields of acid were obtained in this hydrolysis, and the effect of steric hindrance was noted only when both ortho positions were substituted. In the case of 2,6-dibromovanillin (CHO = 1) none of the required acid was isolated, but 87% of the nitrile, m. p. 215°, was recovered.[9]

Experimental Part

5-Bromo-6-chlorovanillin Oxime.—This was obtained in 79% yield by refluxing for one hour a mixture containing 12 g. of the required vanillin, 4 g. of hydroxylamine hydrochloride, 3.2 g. of anhydrous sodium carbonate dissolved in 100 cc. of alcohol and 20 cc. of water, and finally adding water to the hot liquid to precipitate the product. Recrystallization from dilute alcohol gave fine colorless needles, m. p. 203–204° with apparent decomposition.

Anal. Calcd. for $C_8H_7O_3NClBr$: X, 41.17. Found: X, 40.61.

The isomeric 5-chloro-6-bromovanillin oxime was obtained in 81% yield as described above. Crystallization from dilute alcohol gave colorless needles; m. p. 203–204° with decomposition. A mixture of the oximes melted at 200°.

Anal. Calcd. for $C_8H_7O_3NClBr$: X, 41.17. Found: X, 40.65.

Preparation of Acetoxynitriles.—A mixture of the oxime and slightly more than three times its weight of acetic anhydride was gently boiled for an hour under a reflux condenser, and the resulting liquid poured into several volumes of ice and water which was being stirred mechanically. In many instances the product separated as an oil, but neutralization with potassium hydroxide and stirring caused it to solidify. The composition and general properties are recorded in Table I.

Hydrolysis of the Nitriles.—To avoid the difficulty involved in the use of hot alkali solution on glass vessels and the consequent contamination of products with silica attempts were made to hydrolyze the nitriles with 90% sulfuric acid.[10] Experiment showed that this would cause much loss by charring and make it difficult to secure any pure product. The method adopted was to boil the nitrile with 6 *N* potassium hydroxide solution under a return condenser until no more ammonia was evolved. The cooled mixture was then acidified by concentrated hydrochloric acid, cooled again, the precipitated acid collected and crystallized from a suitable solvent. The effect of halogen substitution in the time required for hydrolysis, and the composition and properties of the acids are indicated in Table II.

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(8) Raiford and others, THIS JOURNAL, **52**, 4576 (1930).

(9) The composition was checked by bromine determination. *Anal.* Calcd. for $C_8H_5O_2NBr_2$: Br, 52.11. Found: Br, 51.97.

(10) Sudborough, *J. Chem. Soc.*, **67**, 602 (1895).

TABLE I

3-METHOXY-4-ACETOXYBENZONITRILE AND HALOGEN SUBSTITUTION PRODUCTS

Substituents	Yield, %	Solvent	Crystal form	Formula	M. p., °C.	Halogen analyses, % Calcd.	Found
Acetoxyvanillonitrile (unsubstituted)	94[a]	Water	Colorless needles	$C_{10}H_9O_3N$	110	...	...
2-Bromo-	Nearly quant.	Dil. alc.	Colorless needles	$C_{10}H_8O_3NBr$	71– 72	29.63	29.53
2,6-Dibromo-	98	*n*-Butanol	Nearly colorless needles	$C_{10}H_7O_3NBr_2$	143–144[b]	45.85	45.66
2,5,6-Tribromo-	97	Alc.	Nearly colorless needles[c]	$C_{10}H_6O_3NBr_3$	174–175	56.05	55.86
5-Chloro-	Nearly quant.	Isobutanol	Thick yellow needles	$C_{10}H_8O_3NCl$	133–134	15.73	15.61
6-Chloro-	95	HAc	Fine colorless needles	$C_{10}H_8O_3NCl$	131–132	15.73	15.78
5,6-Dichloro-	Nearly quant.	Dil. HAc	Colorless scales	$C_{10}H_7O_3NCl_2$	143–144	27.28	26.75
5-Bromo-6-chloro-	Nearly quant.	Dil. HAc	Pale yellow needles	$C_{10}H_7O_3NClBr$	165	37.94	37.91
5-Chloro-6-bromo-	90	Alc.	Colorless powder	$C_{10}H_7O_3NClBr$	176	37.94	37.47

[a] This product was isolated by Marcus [*Ber.*, **24**, 3654 (1891)] but no yield was recorded. [b] A mixture of this and the corresponding oxime, m. p. 144–145°, melted at 115–120°. [c] Exposure to light caused the crystals to develop a grayish-yellow color.

TABLE II

ACIDS OBTAINED BY HYDROLYSIS OF SUBSTITUTED ACETOXYVANILLONITRILES

Substituents	Time, hours	Yield, %	Solvent	Crystal form	Formula	M. p., °C	Halogen analyses, % Calcd.	Found
Unsubstituted	1	93[a]	Alc.	Colorless needles	$C_8H_8O_4$	207–208	...	...
2-Bromo-	4	Nearly quant.	Water	Colorless needles	$C_8H_7O_4Br$	163–164	32.39	32.72
5-Bromo-	2	98[b]	Alc.	Colorless needles	$C_8H_7O_4Br$	231–232[b]	32.39	32.41
5,6-Dibromo-	48	78	Water	Nearly colorless needles	$C_8H_6O_4Br_2$	199–200[c]	49.08	48.80
2,5,6-Tribromo-	54	70	Dil. alc.	Nearly colorless flakes	$C_8H_5O_4Br_3$	231–232 Decomp.	59.25	59.63
5-Chloro-	2	95	Dil. HAc	Fine colorless needles	$C_8H_7O_4Cl$	244–245	17.55	17.45
6-Chloro-	3	78	Dil. HAc	Colorless leaflets	$C_8H_7O_4Cl$	207	17.55	17.66
5,6-Dichloro-	10	Nearly quant.	Water	Straw colored needles	$C_8H_6O_4Cl_2$	184–185[d]	29.92	29.85
5-Bromo-6-chloro-	13	80	Water	Nearly colorless needles	$C_8H_6O_4ClBr$	196–197[e]	41.01	40.84
5-Chloro-6-bromo-	13	85	Very dil. alc.	Straw colored needles	$C_8H_6O_4ClBr$	187–188[f]	41.01	41.12

[a] On record, but not obtained by this method or in this yield. [b] Found, also, for a sample prepared by bromination of vanillic acid. Both samples darken and shrink about 223° and evolve gas slowly at the melting point. Brady and Dunn recorded 221°. They found 179° for 5-bromovanillin oxime, but noted no decomposition in either case. In the present work slow heating caused the oxime to decompose with evolution of gas about 170°; with rapid heating it melts to a clear liquid at 179° and decomposes a few seconds later. [c] Dried to constant weight at 120–130°: 0.3665 g. lost 0.0106 g. Calcd. for $C_8H_6O_4Br_2 \cdot 0.5\ H_2O$: H_2O, 2.69. Found: H_2O, 2.89. [d] Attempts to determine water of hydration directly were unsatisfactory because of slow sublimation on heating. *Anal.* Calcd. for $C_8H_6O_4Cl_2 \cdot 0.5H_2O$: Cl, 28.83. Found: Cl, 28.95. [e] Calcd. for $C_8H_6O_4ClBr \cdot 0.5H_2O$: Hal., 39.74. Found: Hal., 40.01. [f] Calcd. for $C_8H_6O_4ClBr \cdot 0.5H_2O$: Hal., 39.74. Found: Hal., 39.69.

Summary

1. Chlorine and bromine as substituents in vanillin oxime cause no appreciable hindrance in the formation of the acetoxynitriles.

2. The acetoxynitriles may be hydrolyzed by caustic potash solution to give high yields of the corresponding acids, unless both ortho positions are substituted. When the 2,6-dibromo compound was used no acid was obtained but 87% of the nitrile was recovered. So far as examined, the chlorine derivatives are more reactive than the bromine compounds.

3. Each of the four 5,6-dihalogenated vanillic acids studied crystallized from water with half a molecular proportion of solvent of crystallization.

4. Further work is in progress.

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The Resolution of β-Ethoxyamines

BY WALLACE R. BRODE AND I. J. WERNERT

In an earlier paper[1] a method has been described for the synthesis of β-ethoxyamines. The present paper describes the complete resolution of β-ethoxyhexylamine and β-ethoxy-β-phenylethylamine and the partial resolution of β-ethoxybutylamine and β-ethoxyamylamine. The resolution of these amines proved to be extremely difficult. There appeared to be no marked difference in the solubility of the acid tartrate or camphor sulfonate salts of the *d*- and *l*-amines, and in addition there was a tendency to form gels which could not be filtered. In certain of the cases studied, more than twenty fractional crystallizations failed to yield a salt of constant rotation. In other cases a salt of constant rotation was obtained in two or three recrystallizations, and although fifteen to twenty additional crystallizations failed to change its rotation, the activity of the amine recovered from the mother liquor and the complete resolution of the amine by other resolving agents showed that only a partial resolution had been effected.

Considerable doubt may exist as to the completeness of a resolution if a statement indicating the constancy of the rotation of the salt or even the specific rotation of the salt is omitted. If the maximum rotation of the final pure salt were included, the repetition of the resolution by others would be greatly facilitated. A second consideration that is often overlooked in the resolution of asymmetric compounds is a determination of the rotation of the active compound that may be obtained by the hydrolysis of mother liquors which contain the more soluble fraction. In the case of the attempted resolution of β-ethoxy-β-phenylethylamine

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[1] Wernert and Brode, THIS JOURNAL, **54**, 4365 (1932).