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OXIDATION OF 4-ACYLOXY DERIVATIVES OF
CINNAMIC ACID

VICTOR S. WEBSTER AND L. CHAS. RAIFORD

It is known that benzaldehyde (17) and its alkyl, alkoxy and halogen substitution products are easily oxidized to the corresponding acids. In many cases contact with air brings about the change (4).

The presence of hydroxyl as a substituent often makes the aldehyde less reactive toward oxidizing agents. For example, Bücking (3) and Fitting and Rensen (5) reported that *p*-hydroxybenzaldehyde and protocatechuic aldehyde, respectively, are not readily oxidized by potassium permanganate solution, but require fusion with caustic potash to give the related acids. Tiemann (13) found that when vanillin, the 3-methyl ether of protocatechuic aldehyde, is treated with oxidizing agents hardly any change takes place or else complete decomposition occurs, depending on conditions, while Brady and Dunn (2) failed to oxidize 5-bromovanillin with acetic acid solution of chromic acid and also by alkaline solution of potassium permanganate. To obtain the acid in this case recourse was had to a method previously used by Vogl (16) in preparing 5-nitrovanillic acid, which involved alkaline¹ hydrolysis of the corresponding nitrile which, in turn, had been obtained by treatment of the required oxime with acetic anhydride.² If the hydroxyl group is alkylated the product is more easily oxidized, for Tiemann (12) found that methyl- and ethylvanillin are readily converted to the related acids, though he failed to specify the reagents used and the yields obtained. Likewise, Lovecy, Robinson and Sugawara (7) reported that oxidation of an acetone solution of benzylvanillin with potassium permanganate gave an 80 per cent yield of benzylvanillic acid. Though the product was not analyzed they characterized it by conversion into anhydride.

The behavior indicated above is supported by observations made in this Laboratory. Thus, Ravelly (10) found that the treatment of protocatechuic aldehyde with potassium permanganate solution

¹ Attempts in this Laboratory to use the method suggested by Sudborough, in which sulfuric acid is required, [J. Chem. Soc., 67, 602 (1895)] were unsuccessful.

² More recently Raiford and Potter [J. Am. Chem. Soc., 55, 1682 (1933)] tested this method with several vanillin substitution products and obtained yields of 70 to 98 per cent (based on the nitrile used), except where both ortho positions were occupied by bromine, in which case 87 per cent of the starting material was recovered. Apparently the reaction is general.

caused almost complete decomposition, and that the small amount of residue left was resinous and could not be identified; while the corresponding dimethyl derivative (methylvanillin) gave, under the same conditions, a 65 percent yield of the required acid.

A second method by which an aromatic acid may be obtained from the aldehyde involves conversion of the latter into the corresponding β -arylacrylic (cinnamic) acid, and oxidation of this with a suitable reagent. Several workers (6) have oxidized cinnamic acid with potassium permanganate under various conditions and have obtained benzoic acid and other products, but yields have not always been given. In cases where hydroxyl is a substituent of the phenyl nucleus oxidation of the cinnamic acid is more difficult than otherwise. To oxidize *p*-hydroxycinnamic acid to the related benzoic acid Barth and Schreder (1) found it necessary to heat the starting material with sodium hydroxide to 340°. Of the possible *p*-acyloxy substitution products only one appears to have been tested, viz., the acetyl derivatives of 3-methoxy-4-hydroxycinnamic acid, from which Tiemann and Nagai (15) obtained by oxidation a mixture of acetylvanillin and acetylvanillic acid. They neglected to mention the oxidation agent used, the conditions under which the work was done, and the yields of the respective products.

In this Laboratory (8) Perry found that when 3,4-diacetoxycinnamic acid was oxidized with the calculated quantity of alkaline solution of potassium permanganate protocatechuic aldehyde in small yield only was isolated, but that when the oxidation was carried through in a mixture that was about neutral, and which prevented the loss of the acyl groups, a 50 per cent yield of the corresponding benzoic acid was obtained.

In view of these observations it was of interest to study the relations further. To test the effect of the acyloxy radical in this connection 4-hydroxybenzaldehyde was converted into several *p*-acyloxycinnamic acids and these were oxidized by aqueous or pyridine solutions of potassium permanganate under conditions which prevented the loss of acyl during the reaction. It may be stated at once that the corresponding benzoic acid derivative was obtained in each case, and that, in addition, in one instance, only, a small yield of the related aldehyde was isolated. In this case much degradation took place.

EXPERIMENTAL PART

Acyl derivatives of 4-hydroxycinnamic acid. The required 4-hydroxybenzaldehyde was obtained by purification of Eastman's

technical grade. This was extracted with cold chloroform, the extract filtered, the solvent distilled, and the residue repeatedly crystallized from water. Norite was used in the last treatment. The product was obtained in pale pink needles that melted at 115-116°, which agrees with Reimer and Tiemann's (11) observations.

4-Hydroxycinnamic acid was prepared by directions of Tiemann and Herzfeld (14) modified to the extent that when the reaction was complete the hot mixture was poured into 12 volumes of water, after which sodium hydroxide solution was added to hydrolyze the acetyl derivative completely and avoid the formation of a mixture. The hot liquid was filtered, the filtrate was acidified with concentrated hydrochloric acid, the precipitated acid collected and the remaining filtrate extracted with ether. In this way a yield of 74 percent was obtained. Tiemann and Herzfeld recorded no yield. Recrystallization of the product from water gave nearly colorless needles that melted at 205-206°.

To obtain the desired acyl derivative a solution of p-hydroxycinnamic acid in slight excess of caustic alkali was treated with the required acylating agent. The benzoyl and chlorobenzoyl compounds were prepared by the Schotten-Baumann method, while the remainder were satisfactorily obtained by slowly adding to the alkaline solution of the cinnamate an ether solution of the necessary anhydride or acid chloride, with continued shaking, as directed by Pschorr and Sumuleanu (9). The mixtures were then allowed to stand several hours, and the products that separated were purified by crystallization from suitable solvents. Analytical and other data are given in Table I.

Oxidation of the acyloxy derivatives. A convenient quantity of the acid, usually 5 to 8 grams, suspended in about 100 cc. of water or dissolved in an equal volume of pyridine, was placed in a three-necked flask fitted with a mechanical stirrer, and magnesium sulfate was added to keep the liquid nearly neutral and thus prevent the loss of acyl by hydrolysis. The mixture was stirred continuously at room temperature while a solution of potassium permanganate representing six available atomic proportions of oxygen, dissolved in the liquid indicated, was added from a dropping funnel in about twenty minutes, and the mixture was stirred continuously for several hours thereafter. Sulfur dioxide was next passed in with stirring until the purple color was just discharged, the mixture was filtered by suction, the residue washed and reserved for further study.

Table I—Acyl Derivatives of 4-Hydroxycinnamic Acid.

Acyl Radical	Yield percentage	Crystal Form	M.P. °C.	Formula	Analyses			
					Halogen percentage		Nitrogen percentage	
					Calcd.	Found	Calcd.	Found
Acetyl-	Nearly quant. ^a	Colorless Needles ^b	195-196	C ₁₁ H ₁₀ O ₄
Benzoyl-	Nearly quant.	Colorless Leaflets ^c	232-233 ^d	C ₁₆ H ₁₂ O ₄
3-Chloro-	90	Colorless Leaflets	222-223	C ₁₆ H ₁₁ ClO ₄	11.73	11.51
4-Chloro-	95	Colorless Plates	224-225	C ₁₆ H ₁₁ ClO ₄	11.73	11.50
3-Bromo-	70	Nearly Colorless Needles	219-220	C ₁₆ H ₁₁ BrO ₄	23.05	23.33
4-Bromo-	Nearly quant.	Colorless Leaflets	243-244	C ₁₆ H ₁₁ BrO ₄	23.05	23.08
3-Nitro-	75	Nearly Colorless Needles	240-241	C ₁₆ H ₁₁ NO ₆	4.47	4.43
4-Nitro-	70	Colorless Needles	232-233	C ₁₆ H ₁₁ NO ₆ ^e

a. This product was analyzed by Tiemann and Herzfeld [Ber., 10, 66 (1877)] who prepared it in a different way and did not report a yield.

b. Crystallized from water.

c. Crystallized from alcohol. These following were crystallized from acetic acid.

d. Identified by conversion into the methyl ester, m.p., 130-131°, and compared with a specimen prepared as directed by Power and Salway [J. Chem. Soc., 97, 236 (1910)] m.p., 130-131°. These authors recorded 129° and a satisfactory analysis. Preparation of the compound in question by benzoylation of methyl 4-hydroxycinnamate, m.p., 137-138°, as found by Zincke [Ann., 322, 224 (1902)] gave a product that melted at 130-131°. A mixture of this and the product under consideration melted without depression. Our product was further identified by hydrolysis to 4-hydroxycinnamic acid, m.p., 206°. Power and Salway reported that hydrolysis of their compound, m.p., 129°, gave a product that melted at 215°.

e. Identified by conversion into the methyl ester by heating a mixture of the acid, methyl alcohol and sulfuric acid. This ester, m.p., 203-204°, was compared with a sample prepared as previously described by Konek and Pacsu [Ber., 51, 857 (1918)] by treatment of the methyl ester of 4-hydroxycinnamic acid, note d, with p-nitrobenzoyl chloride. The products melted together without depression.

Table II—Substituted Benzoic Acids Obtained by Oxidation of Acyl Derivatives of 4-Hydroxycinnamic Acids.

Acyl Radical	Solvent Used to Extract Product	Yields of Acylbenzoic Acid	Formula	M. P. °C.	Analyses			
					Halogen		Nitrogen	
					Cal.	Found	Cal.	Found
Acetyl ^a	Ether	90		184-185 ^b				
Benzoyl ^a	Ether	87		220 ^c				
3-Chlorobenzoyl-	Ether	71		216 ^d				
4-Chloro-	Ethyl Acetate	90		239-240 ^d				
3-Bromo-	Ethyl Acetate	83		211-212 ^d				
4-Bromo-	Iso-Propyl Benzoate ^e	79	C ₁₁ H ₉ BrO ₂	250-251	24.92	24.95		
3-Nitro-	Ethyl Acetate	61	C ₁₁ H ₉ NO ₃	252-253 ^f			4.87	4.84
4-Nitro ^a	Chloroform	16	C ₁₄ H ₉ NO ₃	272-273			4.87	4.89
		15	C ₁₁ H ₉ NO ₂	199-200 ^g				
		(Aldehyde)						

a. Oxidized in aqueous mixtures. Others were carried out in pyridine solution.

b. Klepl [J. prakt. Chem., 2, 28, 211 (1883)] found 185° and satisfactory analysis for this product.

c. Vorländer and Gahren [Ber., 40, 1968 (1907)] recorded 220-222°, but gave no method of preparation or identification; Francis and Nierstein [(Ann., 382, 196 and 201 (1911)] and Albright [J. Am. Chem. Soc., 39, 822 and 824 (1917)] mentioned the acid but gave no further data. Its composition, structure and molecular weight were determined by Raiford and Milbery [*ibid.*, 56, 2729 (1934)]

d. 217-218° was found by Raiford and Milbery, loc. cit. who recorded the values here found and satisfactory analyses for the next two.

e. This must be distilled under reduced pressure to avoid decomposition of any residue.

f. Francis and Nierstein [loc. cit.] recorded 273-274°.

g. Isolated from manganese dioxide residue and identified by comparison with the product previously synthesized by Raiford and Milbery.

The combined filtrate and washings were extracted with ether, the extract dried with anhydrous sodium sulfate, and the solvent distilled. No residue remained. The filtrate was acidified with dilute sulfuric acid, extracted as indicated, the acid recovered, purified by crystallization from a suitable solvent and identified by comparison with a reference compound prepared in a different way.

The manganese dioxide residue was dried, pulverized and extracted with a suitable solvent. Distillation of the latter left nothing, except in the case of the 4-nitrobenzoyl derivative, where a small portion of the aldehyde was recovered.

In cases where pyridine was used as a solvent, the excess of permanganate was discharged by sulfur dioxide as before, the mixture was filtered and the residue was washed with pyridine. The mixed filtrate and washings were concentrated to about one-fourth the original volume, diluted with three volumes of water, rendered acid with dilute sulfuric acid and extracted with ether (A). The manganese dioxide residue was suspended in about 250 cc. of water, sulfur dioxide passed in as long as change took place, and the liquid extracted with ether (B). These extracts were mixed, the solvent distilled off, the residue dissolved in a suitable liquid (Table II), the solution repeatedly extracted with a solution of sodium bicarbonate. The final organic layer in each case was dried and the solvent distilled. No residue remained. The bicarbonate solution was acidified, the mixture extracted with ether, the solvent was evaporated and the acids thus obtained were identified by mixed melting point determinations with reference compounds prepared in other ways for this purpose, and by analyses when necessary. Data for them are given in Table II.

SUMMARY

1. A number of p-acyloxycinnamic acids have been prepared and oxidized by potassium permanganate in neutral solution. In every instance the required substituted benzoic acid was obtained. In the case of the 4-nitrobenzoyl derivative a mixture of acid and aldehyde was formed, and much degradation occurred.

2. The results indicate that the resistance to oxidation in the cases of p-hydroxybenzaldehydes and related cinnamic acids may be offset by acylation of hydroxyl.

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