[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

FORMATION AND PROPERTIES OF AZLACTONES OBTAINED FROM VANILLIN SUBSTITUTION PRODUCTS

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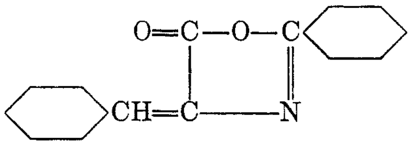
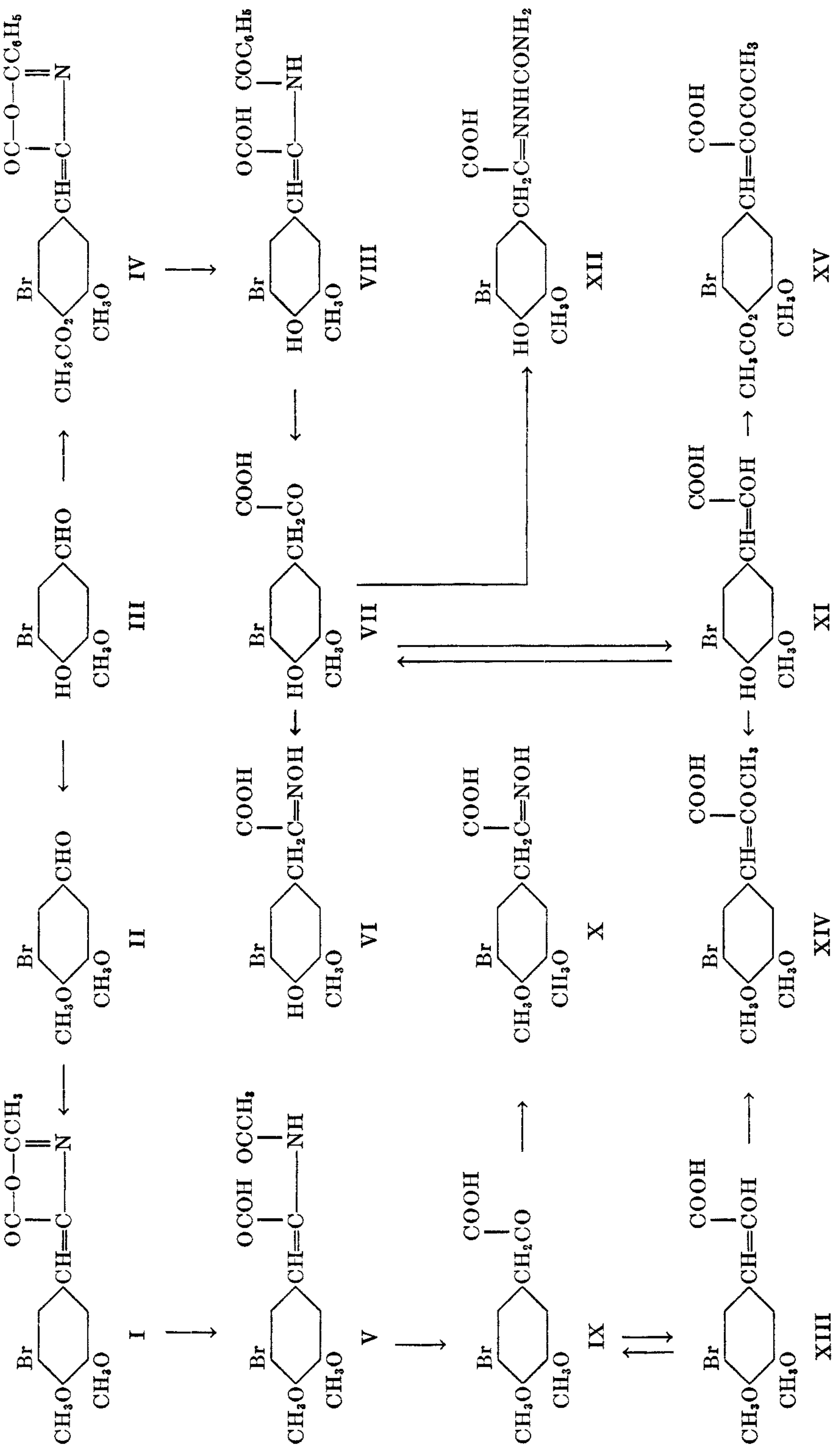
The condensation of aromatic aldehydes with hippuric acid under the influence of acetic anhydride, first noted by Plöchl (1), was studied more intensively by Erlenmeyer and students (2) who established the structures of the products. With benzaldehyde they obtained the inner ester of α-benzoylamidocinnamic acid, designated in the current edition of Beilstein (3) as 2-phenyl-4-benzaloxazolone-5, but more commonly known as an azlactone (4). When a hydroxy aldehyde is used as starting material the corresponding acetyl derivative is obtained.



These azlactones undergo a number of interesting reactions. Warming the compound with caustic alkali solution for a short time opens the ring to give the related α-acylamidocinnamic acid. Heating the latter with acetic anhydride closes the ring to give the azlactone once more. Heating an alcoholic solution of the azlactone with sulfuric acid opens the ring and gives the ester of the acylamidocinnamic acid. Heating the ester with acetic anhydride does not give the azlactone.

Prolonged treatment of these azlactones with boiling caustic alkali solution not only opens the ring but decomposes the α-acylamidocinnamic acid to give ammonia, the acid represented in the acyl radical and the pyruvic acid related to the aldehyde used in preparing the azlactone. In the case of compound IV, Figure 1, obtained from 5-bromovanillin and hippuric acid, the final products obtained were ammonia, benzoic acid, and 3-methoxy-4-hydroxy-5-bromophenylpyruvic acid, VII. The last-named product, like the mother substance, first obtained by Plöchl (1) and studied further by Wislicenus (5), by Erlenmeyer (6), and by Dieckmann (7), was found to exhibit tautomerism. In the present work the keto form was identified by conversion of the acid into an oxime, VI, and a semicarbazone, XII, respectively. Warming the acid with acetic anhydride gave a diacetyl derivative, XV, which was strongly acidic to litmus and soluble in cold dilute sodium carbonate solution, indicating an exposed carboxyl group, thus characterizing enolic form XI. This form was further identified by its reaction with dimethyl sulfate which introduced two alkyl groups to give a trimethyl derivative, XIV, which was also obtained by another route that proved its structure. Following the suggestions of Erlenmeyer and Frühstück (8) 5-bromoveratraldehyde, II, was condensed with aceturic acid, prepared and purified as directed by Radenhausen (9), to give azlactone I, which was

FIGURE 1



I II III IV V VI VII VIII IX X XI XII XIII XIV XV treated with alkali solution, as explained above for the hippuric acid derivative. The resulting α-acylamidocinnamic acid was converted into pyruvic acid IX. Treatment of the latter with dimethyl sulfate introduced one methyl group and gave product XIV. The relations are shown in Figure 1.

EXPERIMENTAL

Azlactones obtained from hippuric acid and vanillin substitution products. To check the method (1) an equimolecular mixture of vanillin, hippuric acid, anhydrous sodium acetate, and 2.5 molecular proportions of acetic anhydride was heated over a steam-bath. The yellow viscous liquid first formed solidified within half an hour but was heated for fifteen minutes longer. The cooled solid was ground with cold alcohol, the mixture was filtered by suction and the residue was washed with water. Crystallization from acetic acid gave small yellow needles that melted at 188–188.5°. The yield was 72%. Mauthner (10) reported 194–195° for a compound made from the same starting materials though he designated the product as a 3-acetoxy-4-methoxy derivative and reported no yield. Harington and McCartney (11) observed the melting point 189°, and obtained a yield of 75%. Data for related products are given in Table I.

TABLE I

AZLACTONES FROM HIPPURIC ACID AND VANILLIN SUBSTITUTION PRODUCTS

SUBSTITUENT IN 4-ACETYLVANILLAL	YIELD, %	CRYSTAL FORM [a]	M.P., °C.	FORMULA	ANALYSES			
					Halogen		Nitrogen	
					Calc'd	Found	Calc'd	Found
5-Chloro-	80	Yellow plates	190.5–191.5	$C_{19}H_{14}ClNO_5$	9.55	9.42	—	—
6-Chloro-	68	Yellow needles	205–206	$C_{19}H_{14}ClNO_5$	9.55	9.53	—	—
5,6-Dichloro-	62	Fibrous masses of needles	239–240	$C_{19}H_{13}Cl_2NO_5$	17.48	17.44		
5-Bromo-	70	Yellow needles	191–191.5	$C_{19}H_{14}BrNO_5$	19.23	19.34	3.36	3.42
6-Bromo-	71	Silky yellow needles	211	$C_{19}H_{14}BrNO_5$	19.23	19.23	3.36	3.34
5,6-Dibromo-	51[b]	[c]	264	$C_{19}H_{13}Br_2NO_5$	32.32	32.21	—	—
2,5,6-Tribromo-	72[d]	Granules	190.5–191	$C_{19}H_{12}Br_3NO_5$	41.81	41.72	—	—
4-Methyl-5-bromo-	62	Yellow powder	167.5–168.5	$C_{18}H_{14}BrNO_4$	20.61	20.51	—	—
5-Iodo-	71	Yellow plates	180–181	$C_{19}H_{14}INO_5$	27.42	27.72	—	—

[a] These products were crystallized from acetic acid.
[b] Purified by extraction of foreign materials with acetic acid.
[c] Due to low solubility in all solvents tried this was not obtained in crystalline form.
[d] This represents crude product; other figures are for purified materials.

2-Bromohippuric acid. Hildebrandt (12) claims to have isolated this compound from the urine of a dog that had been fed 2-bromotoluene, and reported the melting point 153°. Novello, Miriam, and Sherwin (13) obtained by the action of 2-bromobenzoyl chloride on glycocoll a product that melted at 192–193°, but reported no yield. In our work the acid was prepared from the required acyl chloride by Baum's (14) general method. A 70% yield of nearly colorless short thick needles, m.p. 193–194°, was obtained.

Anal. Calc'd for $C_9H_8BrNO_3$: Br, 31.00; N, 5.42.
Found: Br, 30.93; N, 5.37.

Data for azlactones obtained from this acid are given in Table II.

Azlactones from aceturic acid. The mother substance of the derivatives reported here was obtained by Erlenmeyer and Frühstück (8) who heated a mixture of equimolecular proportions of glycine, benzaldehyde, and anhydrous sodium acetate with three proportions of acetic anhydride. Their product melted at 146–147°, and gave a good analysis. No yield was recorded. In the present work a 70% yield of that product, m.p. 149–150°, was obtained by the method specified, with the exception that the glycine was replaced by a purified sample of aceturic acid prepared by Radenhausen's (9) method. Compounds obtained by condensation of this with vanillin substitution products are shown in Table III.

TABLE II

AZLACTONES FROM 2-BROMOHIPPURIC ACID

SUBSTITUENTS IN 4-ACETYLVANILLAL	YIELD, %[a]	CRYSTAL FORM[b]	M.P., °C.	FORMULA	HALOGEN ANALYSES	
					Calc'd	Found
Unsubst.	61	Yellow powder	158.5–159.5	$C_{19}H_{14}BrNO_5$	19.23	19.26
5-Bromo-	65	Yellow powder	187–188	$C_{19}H_{13}Br_2NO_5$	32.32	32.01
6-Bromo-	62	Yellow needles	197–198	$C_{19}H_{13}Br_2NO_5$	32.32	32.15
5,6-Dibromo-	62	Yellow powder	225–226	$C_{19}H_{12}Br_3NO_5$	41.81	41.77
2,5,6-Tribromo-	28	Yellow powder	189–191	$C_{19}H_{11}Br_4NO_5$	49.00	48.96

[a] These figures refer to purified materials.

[b] All compounds were crystallized from acetic acid.

TABLE III

AZLACTONES OBTAINED FROM ACETURIC ACID

SUBSTITUENT IN VANILLAL RESIDUE	YIELD %[a]	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES, HALOGEN	
						Calc'd	Found
5-Chloro-	55	Ethanol	Yellow needles	203–204	$C_{14}H_{12}ClNO_5$	11.46	11.25
4-Methyl-5-chloro-	[b]	Dilute ethanol	Yellow needles	169–170	$C_{13}H_{12}ClNO_4$	12.61	12.56
5-Bromo-	72	Ligroin	Yellow plates	206–207	$C_{14}H_{12}BrNO_5$	22.59	22.40
4-Methyl-5-bromo-	70	Dioxane	Yellow plates	162–163	$C_{13}H_{12}BrNO_4$	24.54	24.40
6-Bromo-	[b]	Ethanol	Yellow leaflets	119–120	$C_{14}H_{12}BrNO_5$	22.59	22.79
5-Iodo-	27	Acetic acid	Yellow plates	196–197	$C_{14}H_{12}INO_5$	31.67	31.42

[a] Figures refer to purified materials.

[b] Resinous material made purification difficult and caused much loss. The yield could not be determined.

α-Benzoylamidoferulic acid (15). A mixture of 3.36 g. of the azlactone obtained from vanillin and hippuric acid and 300 cc. of approximately 3% solution of potassium hydroxide was slowly heated just to the boiling point, dilute hydrochloric acid was added to the cooled solution, and the colorless solid that separated was collected. Crystallization from

60% ethanol gave colorless prisms that melted at 208.5–209.5°. Sugii (16) reported 205°. A mixture of two grams of this acid and 1.5 cc. of acetic anhydride was heated on a steam-bath for fifteen minutes, the remaining anhydride was distilled under reduced pressure, the residue was boiled for a few minutes with 50 cc. of water, and the solid was collected. Crystallization from acetic acid gave yellow needles, m.p. 188–189°, that did not depress the melting point of the starting azlactone. Data for other ferulic acids are given in Table IV.

Ethyl ester of α-benzoylamino-5-bromoferulic acid. To a mixture of 7.2 g. of the required azlactone and 12 g. of absolute ethanol 2.5 g. of concentrated sulfuric acid was added and the whole was heated under a reflux condenser on a steam-bath until all lactone had dissolved, which required about two hours. Unused ethanol was distilled off under reduced pressure at about 65° and water was added to the residue to precipitate the ester. Crystallization from ethanol gave small colorless needles that melted at 196–197°.

TABLE IV

SUBSTITUTED AMIDOFERULIC ACIDS

SUBSTITUENT IN VANILLAL	ACYL IN α-POSITION	YIELD, %[a]	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES, HAL.	
							Calc'd	Found
5-Chloro-	Acetyl	86 (crude)	Water	Colorless plates	212–213	$C_{12}H_{12}ClNO_5$	12.43	12.68
	Benzoyl	Nearly quant.	Dil. ethanol	Colorless needles	227–228	$C_{17}H_{14}ClNO_5$	10.21	10.33
5-Bromo-	Acetyl	[b]	Ethanol	Colorless plates	203–304	$C_{12}H_{12}BrNO_5$	24.24	23.85
	Benzoyl	70	Ethanol 60%	Colorless needles	229–230	$C_{17}H_{14}BrNO_5$	20.40	20.28
4-Methyl-5-Bromo-	Acetyl	70	Water	Colorless needles	198–199	$C_{13}H_{14}BrNO_5$	23.25	23.08
	Benzoyl	[b]	Dilute [c] ethanol	Colorless needles	201–202	$C_{18}H_{16}BrNO_5$	19.70	19.72
5-Iodo	Acetyl	63	Dilute ethanol	Colorless needles	217–218	$C_{12}H_{12}INO_5$	33.68	33.62
	Benzoyl	84	Ethanol	Colorless needles	227–228	$C_{17}H_{14}INO_5$	28.92	29.10

[a] Figures refer to purified materials, unless otherwise indicated.

[b] Removal of resin caused much loss.

[c] By cooling solution obtained by slow addition of alcohol to hot mixture of solid and water.

The composition of this product was checked by preparation in a different way. Ethyl hippurate, obtained in 82% yield by the interaction of silver hippurate and ethyl iodide, was mixed with an ether solution of 5-bromovanillin, a small portion of sodium ethylate was added, the mixture stood for four hours at room temperature, was acidified with acetic acid, and filtered. The solid was extracted with cold ethanol, that dissolved the ester and left unchanged 5-bromovanillin. A mixture of this product and the ester described above melted without depression. Heating the ester with acetic anhydride over a steam-bath for four hours gave no azlactone. Properties of this and related esters are shown in Table V.

3-Methoxy-4-hydroxy-5-bromophenylpyruvic acid. A mixture of 25 g. of the azlactone obtained from 5-bromovanillin and hippuric acid, and 100 cc. of 6 *N* sodium hydroxide solution was placed in a flask attached to a reflux condenser the upper end of which was closed with a stopper bearing a bent tube arranged to conduct volatile material into a measured volume of standard sulfuric acid. The reaction mixture was boiled for six hours, and the ammonia expelled was determined in the usual way. The amount was nearly quantitative. The mixture remaining in the reaction flask was acidified with hydrochloric acid and distilled with steam. The benzoic acid isolated from the distillate represented 94% of that required by theory. The nonvolatile solid remaining in the flask was collected on a filter and washed with a small portion of cold ethanol to remove color and resinous material. Crystallization of the residue from ethanol gave the pyruvic acid, which was identified by the preparation of several derivatives. Data for these are recorded in Table VI.

TABLE V

ESTERS OF α-BENZOYLAMIDO-5-BROMOFERULIC ACID

ADDITIONAL SUBSTITUENT IN VANILLAL	ALKYL PRESENT	YIELD, %	SOLVENT	CRYSTAL FORM	M.P., °C.	COMPOSITION	HALOGEN ANALYSES	
							Calc'd	Found
	Ethyl-	60	Ethanol	Colorless needles	196–197	$C_{19}H_{18}BrNO_6$	19.04	19.14
	Methyl-	72	Ethanol	Colorless powder	205–206	$C_{18}H_{16}BrNO_5$	19.70	19.67
4-Methyl-	Methyl-	68	Ethanol	Colorless needle	119–121	$C_{19}H_{18}BrNO_5$	19.04	19.08

TABLE VI

DERIVATIVES OF 3-METHOXY-4-HYDROXYPHENYLPYRUVIC ACID

COMPOUND	YIELD %[a]	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES, HALOGEN	
						Calc'd	Found
5-Chloro acid	49	Ethanol	Micro-scopic crystals	228–228.5	$C_{10}H_9ClO_5$	14.51	14.63
Oxime	84	Water	Colorless plates	158–159	$C_{10}H_{10}ClNO_5$	13.67	13.61
5-Bromo acid	47	Ethanol	Colorless powder	237.5–239 (decomp.)	$C_{10}H_9BrO_5$	27.68	27.67
Oxime	83	Ethanol	Colorless plates	169 (decomp.)	$C_{10}H_{10}BrNO$	26.31	26.63
Semicarbazone	60	Water	Colorless granules	195–196	$C_{11}H_{12}BrN_3O_5$	23.12	22.96
Diacetate	65	Ethanol	Colorless needles	193–194	$C_{14}H_{13}BrO_7$	21.44	21.11
4-Methoxy-5-bromo acid	37	Ethanol	Colorless powder	175–177	$C_{11}H_{11}BrO_5$	26.50	26.18
Methyl ether	90	Dilute ethanol	Colorless needles	162–163	$C_{12}H_{13}BrO_5$	25.23	25.29
Oxime	78	Ethanol	Colorless needles	143	$C_{11}H_{12}BrNO_5$	25.15	24.94
5-Iodo acid	43	Dilute ethanol	Colorless powder	234–235	$C_{10}H_9IO_5$	37.79	37.63
Oxime	Nearly quant.	Dilute ethanol	Colorless needles	170–171	$C_{10}H_{10}INO_5$	36.18	35.99

[a] Figures refer to purified materials.

SUMMARY

1. Vanillin and many of its substitution products have been condensed with hippuric and aceturic acids, respectively, to give the inner esters of the related α-acylamidocinnamic acids, or azlactones.

2. Treatment of the azlactones for a short period with warm caustic alkali solution opens the lactone ring to give the corresponding α-acylamido acid. Heating the latter with acetic anhydride will close the lactone ring once more.

3. Prolonged treatment of these azlactones with boiling alkali solution decomposes the α-acylamido acids first formed to give ammonia, the acid represented by the acyl radical and the pyruvic acid related to the aldehyde used in preparing the lactone. These pyruvic acids exhibit tautomerism.

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