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

PREPARATION OF α,β-UNSATURATED KETONES AND THEIR REACTION WITH PHENYLHYDRAZINE

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In previous work (1) it was noted that when certain aldehydes and their substitution products were condensed with acetophenone in the presence of sodium hydroxide, as indicated by Schmidt (2) and extended by Claisen and collaborators (3), both mono- and di-acetophenone derivatives were obtained. When the starting ketone contained a substituent, no diacetophenone derivative could be isolated. It was of interest to extend this work to learn if the above observations represent a general kind of behavior, and to gain insight into the possible mechanism of the change. Accordingly, a number of new ketones were prepared by condensation of salicylaldehyde derivatives with acetophenone and some of its substitution products. As before, diacetophenone derivatives were obtained only when the starting ketone was unsubstituted.

The production of the diacetophenone derivative seems to involve the formation of the α,β-unsaturated styryl ketone as a first step. This was indicated by the following facts. When a warm alcoholic solution of equimolecular proportions of 2-benzyloxy-5-bromobenzaldehyde and acetophenone was treated with 50% solution of sodium hydroxide, as indicated under the general method of condensation described below, and the product that separated was removed within three days, there was obtained an almost quantitative yield of yellow solid which, after crystallization, gave pale yellow needles that melted at 162–163°. Analysis for halogen was in good agreement with that required by 2-benzyloxy-5-bromostyryl phenyl ketone. When the experiment was repeated and the reaction mixture was allowed to remain three weeks or longer, the solid that separated first changed on standing to a nearly colorless mass that resembled sand. Purification of this material gave colorless rhombohedra that melted at 99.5–100°. Analysis of this product for halogen indicated 2-benzyloxy-5-bromobenzaldiacetophenone. In a third experiment a portion of the purified monoacetophenone derivative, m.p. 162–163°, and acetophenone were dissolved in alcohol, 50% solution of sodium hydroxide was added, and the mixture was allowed to stand. The product that

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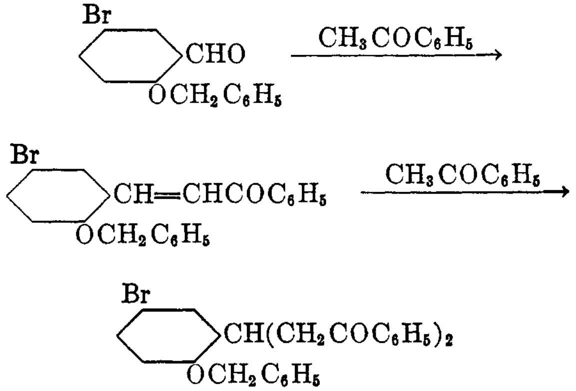
[1] Deceased April 24, 1940.

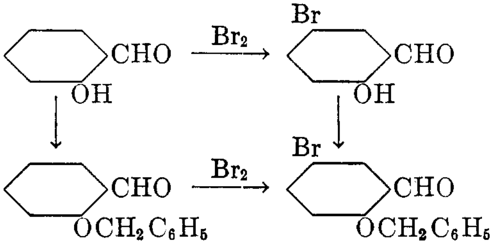
separated was crystallized from alcohol and was found to have the properties of the diacetophenone derivative. A mixture of the two melted without depression. Apparently, acetophenone can add to the ethylenic linkage of the styryl group.



A second purpose of this study was to use the monoacetophenones obtained to test further the action of phenylhydrazine on α,β-unsaturated ketones, since in previous work (4) it was found possible in but few instances to isolate the phenylhydrazones assumed by Auwers and co-workers (5) to be the first products in this reaction. In many cases these hydrazones rearrange immediately to the isomeric pyrazolines. It was hoped that, in accordance with the suggestion of Straus (6), increase in the number of substituents in the reactants would tend to stabilize the hydrazones.

In the preparation of 2-benzyloxybenzaldehyde and its bromine substitution products, used as starting materials in many of the condensations studied here, it was found that the purity of the aldehyde and the conditions of bromination are important factors. Attempts to obtain 5-bromosalicylaldehyde by Piria's (7) method, in which bromine was added to the aldehyde in the absence of a solvent, proved to be unsatisfactory (see experimental part). It was also of interest to note the effect of a solvent. When acetic acid was used, a mixture of 5-bromo- and 3,5-dibromoaldehyde was produced, as noted by Bradley (8) when disalicylaldehyde was treated in the same way. 2-Benzyloxy-5-bromobenzaldehyde was previously obtained by Perkin (9), who reported that it was non-crystalline. He gave no further physical constants and recorded no analysis. The benzyloxybenzaldehyde used by him as starting material had been purified by distillation under ordinary pressure, and repetition of his work was found to give, as he had reported, a brownish oil that did not solidify. Distillation under a pressure of 4 mm. gave a more satisfactory product. Bromination of this in chloroform solution brought about two changes.

Halogen entered position 5 (CHO = 1) and the hydrogen bromide formed split the ether to give 5-bromosalicylaldehyde and benzyl bromide.[2] When the reaction was carried through in acetic acid solution and in the presence of anhydrous sodium acetate, splitting was avoided, and 2-benzyloxy-5-bromobenzaldehyde was obtained. The position taken by halogen was established by preparation of the same compound by benzylation of 5-bromosalicylaldehyde.



In the preparation of the α,β-unsaturated ketones, a modification of Claisen's (3) method was employed. In most cases it was found that they could be obtained by adding a saturated aqueous solution of sodium hydroxide to a warm alcoholic solution of a mixture of the required aldehyde and ketone, and allowing the mixture to stand for a day or two, as indicated by Bablich and Kostanecki (10). A longer period of standing gave, when unsubstituted acetophenone was used, a diacetophenone derivative and some tar. Formation of the latter was favored by elevated temperatures. In all cases the reaction mixture was finally diluted with several volumes of water, and acidified with hydrochloric acid to set free the new ketone. In a number of cases when low yields were obtained by this procedure the method of Glaser and Tramer (11) was tried. It did not give better results.

In the preparation of these compounds it was also of interest to try to obtain them by two routes. It might be supposed, for example, that 2-hydroxy-3,5-dibromostyryl styryl ketone could be obtained with equal ease by condensing 2-hydroxy-3,5-dibromostyryl methyl ketone with benzaldehyde or by condensing benzalacetone with the required substituted salicylaldehyde. As a matter of experiment it was shown that the first method only was satisfactory. The second, in this and other cases, gave much resinous material and low yields of the desired products.

Several of the ketones described in this report were subjected to the action of phenylhydrazine with the hope of obtaining the related phenyl-

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[2] This behavior has been observed by Raiford and Howland [*J. Am. Chem. Soc.*, **53**, 1057 (1931)] in many similar cases.

hydrazones. Previous work had shown that the most suitable solvent in which to conduct this reaction is glacial acetic acid. Since the solubility of these ketones in the acid at room temperature is low, and because the hydrazones are usually rearranged by hot acid, attempts were made to bring about the condensation in some other solvent. Thus, when 3,5-dibromo-4-hydroxystyryl 4-bromophenyl ketone, dissolved in about 15 times its weight of pyridine, was mixed with slightly more than the calculated amount of phenylhydrazine along with one molecular proportion of acetic acid, and the mixture was allowed to stand at room temperature, the product isolated was identical with that obtained when the ketone and hydrazine were brought together in boiling acetic acid. The hydrazone formed in the first instance must have rearranged rapidly. In another case, however, conducting the condensation in boiling acetic acid for one hour failed to convert the whole of the material into pyrazoline. In this reaction a mixture of 2-hydroxy-3,5-dibromostyryl *p*-anisyl ketone with twelve times its weight of acetic acid and the requisite amount of phenylhydrazine was boiled for one hour. When the mixture was cooled and allowed to stand, it deposited pale brown crystals which melted at 167–170°, and which responded to a color test (17) for hydrazones of this group. From the mother liquor left after the separation of these crystals there was isolated a product which, after further purification, was obtained in colorless needles that melted at 193–194°, which was the pyrazoline. These products gave the same analytical data. When a purified sample of the lower-melting one was boiled for a much longer period with acetic acid it was converted into the higher-melting compound.

TABLE I

BENZALDIACETOPHENONE DERIVATIVES

SUBSTITUENTS IN BENZAL RESIDUE	YIELD %[a]	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	HALOGEN	
						Calc'd	Found
2-Benzyloxy-5-bromo-	56	Toluene-ligroin	Colorless rhombohedra	99.5–100	$C_{30}H_{25}BrO_3$	15.59	15.65
2-Benzyloxy-3,5-dibromo-	79	Acetone	Colorless prisms	147–148	$C_{30}H_{24}Br_2O_3$	27.02	26.60
2-Hydroxy-3,5-dibromo-	80	Alcohol	Colorless needles	120–121	$C_{23}H_{18}Br_2O_3$	31.87	31.77
3,5-Dibromo-4-hydroxy-	28	Alcohol	Colorless needles	154–155	$C_{23}H_{18}Br_2O_3$	31.87	31.74

[a] These values represent purified material.

TABLE II
PHENYL STYRYL KETONES

SUBSTITUENT IN PHENYL	SUBSTITUENT IN STYRYL	YIELD %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES HALOGEN	
							Calc'd	Found
4-Methyl-	2-Hydroxy-5-bromo-	48	Toluene	Brownish needles	188 (decomp.)	$C_{16}H_{13}BrO_2$	25.23	25.15
4-Methoxy-		60	Toluene	Brownish needles	174 (decomp.)	$C_{16}H_{13}BrO_3$	24.03	23.83
4-Chloro-		21	Toluene	Yellow needles	184 (decomp.)	$C_{15}H_{10}BrClO_2$	34.22	34.35
4-Bromo-		50	Toluene	Greenish yellow needles	178–178.5 (decomp.)	$C_{15}H_{10}Br_2O_2$	41.88	41.75
4-Methyl-	2-Methoxy-5-bromo-	78[a]	Toluene-ligroin	Yellow needles	130–131	$C_{17}H_{15}BrO_2$	24.16	24.36
	2-Ethoxy-5-bromo-	nearly quant.	Alcohol-acetone	Yellow needles	144–145	$C_{18}H_{17}BrO_2$	23.18	23.23
Unsubs.	2-Benzyloxy-5-bromo-	81	Alcohol-acetone	Pale yellow needles	162–163	$C_{22}H_{17}BrO_2$	20.35	20.26
4-Methyl-		71	Toluene	Yellow needles	160–161	$C_{23}H_{19}BrO_2$	19.65	19.45
4-Methoxy-		76	Alcohol-acetone	Silver needles	156–158	$C_{23}H_{19}BrO_3$	18.91	19.09
4-Chloro-		24	Dioxane[b]	Yellow needles	158–159	$C_{22}H_{16}BrClO_2$	27.01	26.81
Unsubs.	2-Hydroxy-3,5-dibromo-	55	Alcohol	Long yellow needles	164–165	$C_{15}H_{10}Br_2O_2$	41.86	41.53
2-Chloro-		51	Toluene	Yellow needles	162–163	$C_{15}H_9Br_2ClO_2$	46.95	46.68
4-Chloro-		64	Toluene	Yellow needles	197–200 (decomp.)	$C_{15}H_9Br_2ClO_2$	46.95	46.72
4-Bromo-		67	Alcohol	Yellow powder	205–206 (decomp.)	$C_{15}H_9Br_3O_2$	52.06	51.90

4-Methyl-............		67	Toluene	Yellow needles	178–179 (decomp.)	$C_{16}H_{12}Br_2O_2$	40.40	40.23
4-Hydroxy-..........		31	Alcohol	Orange needles	225–227 (decomp.)	$C_{15}H_{10}Br_2O_3$	40.20	40.30
4-Methoxy-..........		58	Toluene	Yellow powder	189 (decomp.)	$C_{16}H_{12}Br_2O_3$	38.83	38.63
4-Amino-............		18	Alcohol	Brownish flakes	195–196 (decomp.)	$C_{15}H_{11}Br_2NO_2$	40.30	40.45
4-Methyl-............	2-Ethoxy-3,5-dibromo-	45	Alcohol	Yellow plates	136–137	$C_{18}H_{16}Br_2O_3 + 0.5\ C_2H_6O$	35.79	35.74
Unsubs...............	2-Benzyloxy-3,5-dibromo-	8	Ligroin	Yellow needles	111–112	$C_{22}H_{16}Br_2O_2$	33.89	33.87
4-Methyl-............			Acetone	Yellow needles	128–129	$C_{23}H_{18}Br_2O_2$	32.92	32.27
4-Methoxy-..........		88	Acetone	Pale yellow needles	137–137.5	$C_{23}H_{18}Br_2O_3$	31.87	31.94
Unsubs...............	3,5-Dibromo-4-hydroxy-	54	Toluene	Pinkish needles	160–161	$C_{15}H_{10}Br_2O_2$	41.88	41.98
4-Methyl-............		50	Toluene	Yellow needles	175–176	$C_{16}H_{12}Br_2O_2$	40.40	40.41
4-Amino-............		41	Alcohol	Yellow powder	227–228	$C_{15}H_{11}Br_2NO_2$	40.32	40.48
2-Chloro-............		7	Toluene	Gray needles	187–188	$C_{15}H_9Br_2ClO_2$	46.93	46.44

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[a] This represents the crude yield. Other figures refer to purified material. The very low values indicate that many crystallizations were necessary.

[b] When this product was crystallized from alcohol it combined with one-half molecular proportion of solvent. Calc'd for $C_{22}H_{16}BrClO_2 + 0.5C_2H_5OH$: Hal., 25.63. Found: Hal., 25.42.

TABLE III
DISTYRYL KETONES

SUBSTITUENT IN FIRST STYRYL RADICAL	SUBSTITUENT IN SECOND STYRYL RADICAL	YIELD %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES HALOGEN	
							Calc'd	Found
Unsubs.	2-Hydroxy-5-bromo-	10	Toluene ligroin	Yellow plates	179–180 (decomp.)	$C_{17}H_{13}BrO_2$	24.31	24.42
	Methylene-3,4-dioxy-6-bromo-	93[a]	Toluene	Brown needles	147–148	$C_{18}H_{13}BrO_3$	22.40	22.51
	2-Hydroxy-3,5-dibromo-	15	Toluene-ligroin	Yellow leaflets	160–160.5 (decomp.)	$C_{17}H_{12}Br_2O_2$	39.21	39.14
4-Methyl-		11	Toluene	Orange powder	181–182 (decomp.)	$C_{18}H_{14}Br_2O_2$	37.91	38.04
4-Methoxy-		30	Toluene	Yellow needles	171–172 (decomp.)	$C_{18}H_{14}Br_2O_3$	36.52	36.66
4-Nitro-		81	Dioxane-water	Brown powder	216–217 (decomp.)	$C_{17}H_{11}Br_2NO_4$	35.32	35.01
4-Phenyl-		22	Toluene	Orange needles	188–189 (decomp.)	$C_{23}H_{16}Br_2O_2$	33.05	33.53
4-Bromo-		57	Toluene	Yellow needles	193 (decomp.)	$C_{17}H_{11}Br_3O_2$	49.28	49.23
Methylene-3,4-dioxy-6-bromo-		25	Toluene	Green needles	200–201 (decomp.)	$C_{18}H_{11}Br_3O_4$	45.19	45.14
3,5-Dibromo-4-hydroxy-		19	Toluene-ligroin	Greenish powder	205–206 (decomp.)	$C_{17}H_{10}Br_4O_3$	54.98	55.21
2-Benzyloxy-5-bromo-		65	Toluene	Yellow powder	186–187 (decomp.)	$C_{24}H_{17}Br_3O_3$	40.47	40.61
2-Methoxy-3,5-dibromo-		77	Toluene	Yellow needles	202–203 (decomp.)	$C_{18}H_{12}Br_4O_3$	53.69	53.73
2-Benzyloxy-3,5-dibromo-		40	Toluene	Yellow needles	200–201 (decomp.)	$C_{24}H_{16}Br_4O_3$	47.61	47.36
4-Hydroxy-3,5-dibromo-	4-Hydroxy-3,5-dibromo-		Ligroin	Yellow needles	Above 275°	$C_{17}H_{10}Br_4O_3$	54.98	54.49

[a] This represents the crude yield. Other figures refer to purified material. The very low values indicate that many crystallizations were necessary.

TABLE IV

SUBSTITUTION PRODUCTS OF 1-PHENYLPYRAZOLINE

SUBSTITUTED PHENYL OR STYRYL IN POSITION 3	SUBSTITUTED PHENYL IN POSITION 5	YIELD %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES HALOGEN	
							Calc'd	Found
4-Methoxy-	2-Benzyloxy-5-bromo-	69[a]	Toluene	Pale yellow needles	182	$C_{29}H_{25}BrN_2O_2$	15.59	15.85
4-Bromo-	2-Hydroxy-3,5-dibromo-	86	Alcohol	Yellow needles	175–177	$C_{21}H_{15}Br_3N_2O$	43.55	43.38
4-Bromo-	3,5-Dibromo-4-hydroxy-	61[a]	Toluene	Yellow needles	189–190	$C_{21}H_{15}Br_3N_2O$	43.55	43.77
4-Methyl-	2-Benzyloxy-3,5-dibromo-	79[a]	Toluene-ligroin	Yellow needles	183–184	$C_{29}H_{24}Br_2N_2O$	27.77	27.70
4-Methoxy-	2-Hydroxy-3,5-dibromo-	5[b]	Toluene	Colorless needles	193–194	$C_{22}H_{18}Br_2N_2O_2$	31.87	32.34
2-Hydroxy-3,5-dibromo-styryl-	4-Bromo-	Very low[c]	Toluene-ligroin	Yellow needles	238–239	$C_{23}H_{17}Br_3N_2O$	41.59	41.95
2-Hydroxy-3,5-dibromo-styryl-	2-Benzyloxy-3,5-dibromo-	47[a]	Toluene	Brown leaflets	145–155	$C_{30}H_{22}Br_4N_2O_2$	41.98	41.76

[a] These values represent purified material.

[b] Obtained from the mother liquor from which the isomeric hydrazone was crystallized.

[c] The yield of crude product was nearly quantitative, but purification required many crystallizations and involved much loss.

EXPERIMENTAL

5-Bromosalicylaldehyde was first prepared by dropping bromine into salicylaldehyde, as directed by Piria (7), but the method proved to be unsatisfactory due to the fact that the resulting solid enclosed considerable unchanged starting material. When acetic acid was used as a solvent and bromine was added slowly to avoid rise of temperature a mixture of 5-bromo- and 3,5-dibromo- salicylaldehyde was obtained. With chloroform as a solvent, only the monobromo compound was formed Crystallization from alcohol gave colorless prisms that melted at 105–106°. Danckwortt (12) reported 105°.

2-Benzyloxy-5-bromobenzaldehyde was obtained in 72% yield of purified product by benzylation of 5-bromosalicylaldehyde as directed by Perkin (9) for the unsubstituted compound. Crystallization from alcohol gave colorless, spear-pointed crystals that melted at 73–74°.

Anal. Calc'd for $C_{14}H_{11}BrO_2$: Br, 27.49. Found: Br, 27.16.

This product was further identified by its preparation in another way. 2-Benzyloxybenzaldehyde was prepared as directed by Perkin but was purified by distillation under reduced pressure as suggested by Auwers and Walker (13). It boiled at 176–177° at 4 mm. Treatment of an acetic acid solution of this ether with somewhat more than one molecular proportion of bromine, dissolved in acetic acid in the presence of sodium acetate, gave a colorless product which, after crystallization from alcohol, melted at 72.5–73.5° and did not depress the melting point of the compound described above. The yield was 80%.

3,5-Dibromosalicylaldehyde, which was used as starting material for the dibromo series, was obtained in purified form in yields of 70% or higher by following the method outlined by Lindemann and Forth (14). It separated in pale yellow needles that melted at 82–83°. Brewster (15) found 81–82°, but Lindemann and Forth reported 85°.

2-Methoxy-3,5-dibromobenzaldehyde. Twenty-four grams of the required dibromosalicylaldehyde was alkylated with dimethyl sulfate as directed by Baeyer and Villiger (16), taking care to keep the mixture alkaline. The product was collected on a filter and washed to remove possible unchanged starting material in the form of the sodium salt. Crystallization from alcohol gave long colorless needles that melted at 92–93°. The yield was 73%. Some starting material was recovered.

Anal. Calc'd for $C_8H_6Br_2O_2$: Br, 54.42. Found: Br, 54.63.

The corresponding ethyl ether was obtained by gradual addition of ethyl iodide to an alcoholic solution of potassium hydroxide and the necessary dibromosalicylaldehyde while the mixture was heated over a vigorously boiling water-bath. The liquid was then refluxed for two hours, after which volatile material was distilled off. Addition of water to the residue precipitated a yellowish solid. Crystallization from alcohol gave pale yellow tablets that melted at 86–87°. The yield of purified product was 61%. Some starting material was recovered from the mother liquor.

Anal. Calc'd for $C_9H_8Br_2O_2$: Br, 51.92. Found: Br, 51.97.

2-Benzyloxy-3,5-dibromobenzaldehyde. One molecular proportion of benzyl chloride was added to a mixture of alcoholic potash and the required dibromosalicylaldehyde, the whole was refluxed for an hour, and allowed to cool. The solid that separated was crystallized from alcohol from which it was obtained in colorless needles, m.p. 109.5–110.5°. The yield of purified product was 66%.

Anal. Calc'd for $C_{14}H_{10}Br_2O_2$: Br, 43.24. Found: Br, 43.03.

Derivatives of these compounds are indicated in tables I, II, III, and IV.

SUMMARY

1. Several derivatives of salicylaldehyde have been condensed with acetophenone and a number of its substitution products. When acetophenone contains no substituent the α,β-unsaturated ketone first formed may add a molecule of the starting ketone to give a diacetophenone derivative. This result is favored by long standing of the reaction mixture.

2. Seven of these α,β-unsaturated ketones whose structures seemed favorable to the formation of stable hydrazones were subjected to the action of phenylhydrazine. The hydrazone was isolated in only one case. In all other instances the required rearrangement product was obtained.

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