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

CONDENSATION OF VANILLIN SUBSTITUTION PRODUCTS WITH ACETOPHENONE

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RECEIVED OCTOBER 23, 1931 PUBLISHED MARCH 5, 1932

Claisen and collaborators[1] showed that acids, caustic alkalies and sodium alcoholate may be used to condense benzaldehyde with acetone to give mono- and dibenzal derivatives. Kostanecki and Rossbach[2] found that with sodium hydroxide as condensing agent benzaldehyde interacts with acetophenone to give benzalacetophenone, benzaldi- and triacetophenones. Yields are not given.

The condensation of vanillin and acetophenone by means of 50% caustic alkali solution at room temperature was studied by Nomura and Nozawa,[3] who obtained a mono- and a diacetophenone derivative. Pearson[4] repeated this work with a "rather more dilute caustic soda" and reported only a monoacetophenone derivative when the experiment was done in winter and the reaction mixture was allowed to stand for seven days; in summer the condensation was complete at the end of three days, and both mono- and diacetophenone derivatives were obtained. In view of these results it was of interest to test the effects of substituents in the starting aldehyde on this condensation.

During the last few years all chlorine and bromine substitution products of vanillin required by theory have been prepared in this Laboratory and condensed with typical amino compounds.[5] Interference with the reaction was noted only in those cases where both positions adjacent to the aldehyde group were substituted, and even then the hindrance was much less than expected. In the benzoin condensation, however, recent work[6] indicates that substituents in positions ortho to the aldehyde radical hinder the reaction. On this account it was desired to condense the halogenated vanillins with acetophenone under the conditions indicated by Schmidt[7] and elaborated by Claisen. It was also of interest to test Pearson's conclusions regarding the kinds and amounts of products formed in terms of variation of time and temperature, and to try to devise a

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[1] Claisen and others, *Ber.*, **14**, 349, 2463 (1881); **20**, 657 (1887); *Ann.*, **223**, 137 (1884).

[2] Kostanecki and Rossbach, *Ber.*, **29**, 1488, 2245 (1896).

[3] Nomura and Nozawa, *Rep. Tohôku Univ.*, **7**, 79 (1918).

[4] Pearson, *Pharm. J.*, **103**, 79 (1919).

[5] Raiford and Lichty, THIS JOURNAL, **52**, 4576 (1930). Other important references are given in that report.

[6] Raiford and Talbot, *ibid.*, **54**, 1092 (1932).

[7] Schmidt, *Ber.*, **14**, 1459 (1881).

more suitable method of preparation for these products. It may be stated at once that repetition of Pearson's experiments[8] in summer and in winter gave both mono- and diacetophenone derivatives.[9] Much time was saved and equally good results were obtained by refluxing the reaction mixtures for one and one-half hours instead of allowing them to stand for longer periods at room temperature.

Experimental Part

The vanillin substitution products were prepared in accordance with the methods already published from this Laboratory. Unless otherwise indicated in the tabular summaries the condensations were carried out as follows. Ten grams each of the substituted vanillin and acetophenone were dissolved in 75 cc. of alcohol, 20 cc. of a 25% solution of sodium hydroxide added, the mixture refluxed for about ninety minutes, cooled, and acidified with hydrochloric acid. This precipitated a mixture of the mono- and diacetophenone derivatives. When this mixture was dissolved in alcohol and the solution allowed to cool, nearly all of the monoacetophenone derivative separated out. The filtrate was heated, diluted, and again cooled to precipitate the diacetophenone compound. The methods of purification and the analytical data are given in the accompanying tables.

TABLE I

VANILLALACETOPHENONE DERIVATIVES

Substituted vanillal	Yield, %	M. p., °C.	Formula	Analyses Halogen, % Calcd.	Found.
2-Bromo-	18[a]	114–115[b]	$C_{16}H_{13}O_3Br$	24.02	24.02
5-Bromo-	33	124–125[c]	$C_{16}H_{13}O_3Br$	24.02	24.22
6-Bromo-	52[d]	172–173	$C_{16}H_{13}O_3Br$	24.02	24.09
2,5-Dibromo-	15	145–146[e]	$C_{16}H_{12}O_3Br_2$	38.83	38.21
2,6-Dibromo-	10	159[f]	$C_{16}H_{12}O_3Br_2$	38.83	38.50
5,6-Dibromo-	20	158.5–160[g]	$C_{16}H_{12}O_3Br_2$	38.83	38.57
2,5,6-Tribromo-	47	174[h]	$C_{16}H_{11}O_3Br_3$	48.83	48.74
5-Chloro-	10	128[i]	$C_{16}H_{13}O_3Cl$	12.30	12.27
6-Chloro-	10	165[j]	$C_{16}H_{13}O_3Cl$	12.30	12.32

[a] Since a mixture of the mono- and diacetophenone derivatives was usually obtained, and separation required many crystallizations, the yields of the purified products only are given. [b] Crystallization from dilute alcohol gave yellow granules. [c] Yellow

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[8] The sparing solubility of 5,6-dibromovanillin in alkali solution seemed to prevent condensation with this derivative. The desired results were obtained by refluxing a glacial acetic acid solution of the reactants with concentrated hydrochloric acid for seven hours according to the general method of Glaser and Tramer [*J. prakt. Chem.*, **116**, 332 (1927)].

[9] Regardless of the relative amounts of aldehyde and ketone employed, a mixture of products was obtained where unsubstituted acetophenone was used. Work now in progress, which will be reported later, suggests that only the monoacetophenone derivatives will be obtained when substituted acetophenones are used as starting material.

granules from slightly diluted alcohol. [d] This product was separated from the diacetophenone described below and formed in the same reaction mixture, as follows: crystallization of the entire mass from slightly diluted alcohol gave a mixture of large yellow crystals and small colorless ones, which was well dried and placed in a "trough" made by creasing a large piece of filter paper. The small crystals adhered to the paper more strongly than the larger ones, which were readily removed by lowering one end of the trough and shaking it gently. This yellow material was subjected to five repetitions of this treatment, and then crystallized five times from alcohol. It separated in prisms. [e] Four crystallizations from dilute alcohol gave nearly colorless needles. [f] Purification required fourteen crystallization from dilute alcohol to give fine yellow needles. [g] Four crystallizations from acetic acid followed by two from dilute alcohol gave yellow needles. [h] Colorless granules after two crystallizations from alcohol. [i] Recrystallization four times from alcohol gave yellow granules. [j] Repeated recrystallization of the reaction product gave yellow prisms.

TABLE II

VANILLALDIACETOPHENONE DERIVATIVES

Substituted vanillal	Yield, %	M. p., °C.	Formula	Analyses Halogen, % Calcd.	Found
2-Bromo-	11[a]	154–155[b]	$C_{24}H_{21}O_4Br$	17.66	17.92
5-Bromo-	17	150–151[c]	$C_{24}H_{21}O_4Br$	17.66	17.81
6-Bromo-	26	137[d]	$C_{24}H_{21}O_4Br$	17.66	17.64
2,5-Dibromo-	7	134–135[e]	$C_{24}H_{20}O_4Br_2$	30.07	30.22
2,6-Dibromo-	7	135[f]	$C_{24}H_{20}O_4Br_2$	30.07	30.23
5,6-Dibromo-	5	163–164[g]	$C_{24}H_{20}O_4Br_2$	30.07	29.90
2,5,6-Tribromo-	6	163[h]	$C_{24}H_{19}O_4Br_3$	39.28	39.22
5-Chloro-	7	151[i]	$C_{24}H_{21}O_4Cl$	8.69	8.64
6-Chloro-	3	151[j]	$C_{24}H_{21}O_4Cl$	8.69	8.57

[a] All yields refer to the purified products. [b] Repeated crystallization from alcohol gave small nearly colorless plates. [c] Colorless needles after several crystallizations from dilute alcohol. [d] Fine colorless needles by repeated crystallization from alcohol. [e] Several crystallizations from dilute alcohol gave nearly colorless fine needles. [f] Repeated crystallization from alcohol gave nearly colorless small plates. [g] Very fine colorless needles from acetic acid. [h] Three crystallizations from glacial acetic acid gave very fine colorless needles. [i] Colorless needles after many crystallizations from dilute alcohol. [j] Several recrystallizations from dilute alcohol gave fine colorless needles.

Summary

1. The bromine and chlorine substitution products of vanillin condense with acetophenone in the presence of sodium hydroxide to give mono- and diacetophenone derivatives.

2. Of the vanillalacetophenones, the three monobromo, the 2,6- and the 5,6-dibromo compounds are yellow; while the 2,5-dibromo and the 2,5,6-tribromo products are practically colorless. The chlorine compounds studied show similar differences. None of the diacetophenone derivatives are colored.

3. Further work is in progress.

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