

REACTIONS OF VANILLIN AND ITS DERIVED COMPOUNDS. XII.¹
BENZYL METHYL KETONES DERIVED FROM VANILLIN
AND ITS RELATED COMPOUNDS^{2, 3}

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In the course of an extended program on the preparation of therapeutically active compounds from vanillin and its related compounds, it was necessary to prepare the substituted benzyl methyl ketones corresponding to vanillin, piperonal, *o*-benzylvanillin, and veratraldehyde. The procedure employed was patterned after that of Kulka and Hibbert (1) who treated vanillin with nitroethane in ethanol in the presence of methylamine as a catalyst to form β -nitroisoeugenol. The β -nitroisoeugenol was then reduced with iron and hydrochloric acid to the oxime which, in turn, was hydrolyzed to vanillyl methyl ketone. Kulka and Hibbert, who worked with very small quantities, found it necessary to hydrolyze the oxime in a second operation. Working with large amounts, we have found that the hydrolysis of the intermediate oxime took place during the work-up of the reduction mixture, and that only the ketone was isolated in every case. The data for the substituted β -nitropropenylbenzenes and for the substituted benzyl methyl ketones are given in Tables I and II, respectively. Table I also includes data for the substituted β -nitropropenylbenzene derived from 5-nitrovanillin.

The ultraviolet absorption spectra of these compounds were determined in 95% ethanol with a Beckman spectrophotometer at minimum slit width. Figure 1 illustrates the changes taking place in the absorption spectra of the intermediates of a representative substituted benzyl methyl ketone synthesis. Except for the spectra of the original aldehydes, very little difference existed between the spectra of the various compounds in each class. The substituted benzyl methyl ketones possessed only a small fraction of the absorption characteristics of their corresponding benzaldehydes and β -nitropropenylbenzenes.

EXPERIMENTAL

All melting points given are uncorrected.

Preparation of substituted β -nitropropenylbenzenes. A solution of 250 g. of vanillin in 900 cc. of 95% ethanol at 20° was treated successively with stirring with 150 cc. of nitroethane, 10 g. of methylamine hydrochloride, and 8 g. of sodium carbonate. After stirring

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TABLE I
 SUBSTITUTED β -NITROPROPENYL BENZENES

NO.	SUBSTITUTED β -NITROPROPENYL BENZENE	YIELD, %	SOLV. ^a	M.P., °C.	FORMULA	ANALYSES			
						C		H	
						Calc'd	Found	Calc'd	Found
1	4-Hydroxy-3-methoxy	72	A	101-102 ^b					
2	3,4-Dimethoxy	54	A	71 ^c					
3	3,4-Methylenedioxy	87	B	97-98 ^d					
4	4-Benzyloxy-3-methoxy	96	C or D	87-88	C ₁₇ H ₁₇ NO ₄	68.21	68.20	5.73	5.74
5	4-Hydroxy-3-methoxy-5-nitro	55 ^e	D	139-140	C ₁₀ H ₁₀ N ₂ O ₆	47.25	47.38	3.97	4.01

^a For recrystallization: A, dilute methanol; B, ethanol; C, petroleum ether; D, methanol. ^b Kulka and Hibbert (1) recorded 101-102°. ^c Kauffmann (2) reported m.p. 73° for the compound which he prepared by condensation of veratraldehyde with nitroethane in the presence of ethylamine with no solvent. ^d β -Nitroisosafrrole melting at 98° was prepared by Knoevenagel and Walter (3) from piperonal and nitroethane in the presence of ethylamine and in the absence of solvent. ^e Long refluxing was necessary to obtain reaction in this case, and the crude precipitate was extracted with 21% sodium bisulfite solution before recrystallization.

 TABLE II
 SUBSTITUTED BENZYL METHYL KETONES

NO. ^a	YIELD, %	BOILING POINT		n_D^t	t, °C.	FORMULA	ANALYSES			
		°C.	MM.				C		H	
							Calc'd	Found	Calc'd	Found
1 ^b	72	126-127	0.3	1.5481	22	C ₁₀ H ₁₂ O ₃ ^c	66.65	66.60	6.71	6.53
2 ^d	90	135	.8	1.5336	26					
3 ^e	72	103-104	.2	1.5400	26					
4 ^f	90	198-200 ^g	1.6	1.5730	24	C ₁₇ H ₁₈ O ₃	75.53	75.47	6.71	6.75

^a The numbers refer to the same substituents noted in Table I. ^b Semicarbazone, m.p. 161°. Kulka and Hibbert (1) prepared vanillyl methyl ketone by hydrolysis of the corresponding oxime and obtained a product boiling at 115° at 0.15 mm., n_D^{25} 1.5444. ^c Anal. CH₃O: Calc'd, 17.22; Found, 17.24. ^d Eastham, Fisher, Kulka, and Hibbert (4) reported veratryl methyl ketone, b.p. 118° at 0.22 mm., n_D^{25} 1.5330. ^e Semicarbazone, m.p. 162° (from ethanol). Anal. Calc'd for C₁₁H₁₃N₃O₃: C, 56.16; H, 5.47. Found: C, 56.16; H, 5.67. Oxime, m.p. 87° (from ethanol). Wallach and Muller (5) prepared piperonyl methyl ketone by hydrolysis of the corresponding oxime and obtained the following constants: n_D^{25} 1.5430; semicarbazone, m.p. 159-160°; oxime, m.p. 86-87°. ^f Semicarbazone, m.p. 156° (from ethanol). Anal. Calc'd for C₁₈H₂₁N₃O₃: C, 66.04; H, 6.47. Found: C, 66.11; H, 6.58. Oxime, m.p. 116-117° (from dilute ethanol). Anal. Calc'd for C₁₇H₁₉NO₃: C, 71.76; H, 6.71. Found: C, 71.47; H, 6.80. ^g Scratching the oil caused its crystallization with the evolution of considerable heat. Recrystallization from dilute ethanol gave white needles melting at 61°.

for a short time, the mixture was allowed to stand 2 weeks in the dark. The mixture was stirred into 7 liters of water, the precipitate was filtered, washed with water, and air-dried. It was dissolved in the minimum amount of methanol, filtered, and diluted with water,

yielding translucent crystals melting at 99–100°. Another purification from methanol and water raised the melting point to 100–101°. The yield of β -nitroisoeugenol was 272 g. or 79%.

In the preparation of all of the other β -nitropropenylbenzenes listed in Table I, the original reaction mixture, after standing at room temperature, was cooled in the refrigerator. The desired crude product was obtained as a crystalline precipitate.

Preparation of substituted benzyl methyl ketones. In a 5-liter 3-necked flask equipped with a stirrer and reflux condenser were placed 1000 cc. of ethanol and 110 g. of β -nitroisoeugenol.

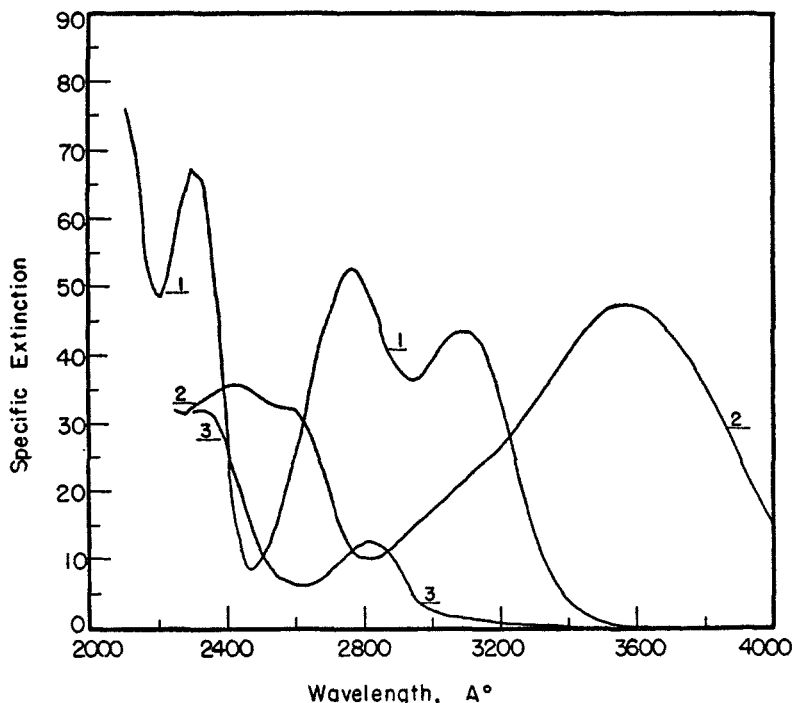


FIGURE 1. ULTRAVIOLET ABSORPTION CURVES OF 4-BENZYLOXY-3-METHOXYBENZYL METHYL KETONE AND ITS INTERMEDIATES. 1. *o*-Benzylvanillin; 2. 4-Benzyloxy-3-methoxy- β -nitropropenylbenzene; 3. 4-Benzyloxy-3-methoxybenzyl methyl ketone.

The mixture was heated with stirring and, when the nitroisoeugenol was dissolved, 2500 cc. of hot water was added. With heating and vigorous stirring, 200 g. of reduced iron powder and 8 g. of hydrated ferric chloride were added. With continued stirring 100 cc. of concentrated hydrochloric acid was added slowly. The hydrochloric acid caused a violent reaction which subsided after about 5 minutes; the mixture was refluxed with stirring for two hours and then distilled under reduced pressure until approximately 2 liters of distillate was collected. The residue was filtered, and the fluffy iron oxide was washed thoroughly with hot water and then with ether. The combined filtrate and washings were acidified strongly with hydrochloric acid and extracted with ether. The ether was dried and distilled to yield a light oil which was fractionated *in vacuo* to give 68 g. of vanillyl methyl ketone boiling at 126–127° at 0.3 mm.

The benzyl methyl ketones listed in Table II were prepared from the corresponding β -nitropropenylbenzenes by almost identical procedures.

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SUMMARY

Some old and new β -nitropropenylbenzenes and benzyl methyl ketones have been prepared from vanillin and some of its related compounds. The ultraviolet absorption spectra of these compounds have been determined.

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