

[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORIES OF THE MONSANTO CHEMICAL COMPANY]

The Reaction of Salicylic Acids with Aldehyde Diacetates

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Previously known acid-catalyzed reactions between salicylic acid and aldehydes or aldehyde derivatives have resulted solely in alkylation of the nucleus.¹ In the preceding paper,² however, it was shown that salicylic acid will react with vinyl acetate to give 2-methyl-4-keto-1,3-benzodioxane. A new synthesis of this material in better yield (87%) is now afforded by the reaction of salicylic acid with ethylidene diacetate. Since many aldehyde diacetates are readily available in good yield from aldehydes and acetic anhydride, this technique has now been explored as a method of introducing substituents other than the methyl group in the 2-position.

The method has proved to be very satisfactory in the case of aromatic aldehydes or α,β -unsaturated aliphatic aldehydes. Thus, benzal diacetate and several nuclearly substituted benzal diacetates have been condensed easily in good yields with salicylic acid in the presence of a trace of sulfuric acid to give 2-aryl-4-keto-1,3-benzodioxanes.³ Piperonal, *m*-nitro-, *o*-chloro- and 2,6-dichlorobenzal diacetates all react satisfactorily. In the case of the last compound, it is interesting to note that the two ortho chlorine atoms did not offer sufficient steric hindrance to slow down the rate of reaction appreciably. Benzal diacetate and piperonal diacetate were also condensed satisfactorily with *o*-cresotinic acid and with thio-salicylic acid, in the latter case giving a thioxane analogous to that formed from vinyl acetate and thio-salicylic acid.²

Furfural diacetate formed principally insoluble black polymeric products under these conditions, although a small yield of 2-furyl-4-keto-1,3-benzodioxane was isolated. The 2-styryl analog was obtained in good yield from cinnamal diacetate and salicylic acid. With crotonal diacetate, the 2-propenyl derivative was obtained in much lower yields. The reaction appeared to proceed rapidly (as evidenced by the evolution of acetic acid), but a large portion of the product proved to be non-volatile and polymeric in nature. In the case of allylidene diacetate a side-reaction leading to the formation of acetylsalicylic acid appeared to predominate although a small yield of 2-vinyl-4-keto-1,3-benzodioxane was obtained. The by-product undoubtedly was formed by the reaction of salicylic acid with acetic anhydride

which had been formed by dissociation of the allylidene diacetate.

In the case of aliphatic aldehyde diacetates other than ethylidene diacetate, little or none of the desired product was obtained. Here the predominant reaction was not one of ester interchange but simply one of dissociation of the diacetate back to the aldehyde and acetic anhydride. The diacetates of formaldehyde, propionaldehyde, butyraldehyde and chloral all behaved in this manner. However, the success of the condensation reaction does not appear to be explained simply by the ease of dissociation of the aldehyde diacetates since Coffin⁴ and co-workers have shown that the rates of dissociation of the diacetates of aromatic aldehydes, furfural and crotonaldehyde are approximately six times that of ethylidene diacetate which, in turn, is dissociated at twelve times the rate of methylene diacetate.

The physical constants and other pertinent data for this series of compounds are presented in Table I.

An attempt was made to extend this reaction to the preparation of methylene cyclic esters of malonic acid since the latter resembles salicylic acid with reference to the configuration of the functional groups. The reaction appeared to proceed normally, the theoretical amount of acetic acid being liberated at 40–70°. However, the only neutral substance isolated was 5% of benzylidene benzalmalonate, together with a 37% yield of benzylidene malonic acid. Analogous results are reported by Michael and Weiner⁵ in the sulfuric acid-catalyzed reaction of cinnamaldehyde, malonic acid and excess acetic anhydride.

Experimental

Aldehyde Diacetates.—Benzal diacetate,⁶ m. p. 44°, *o*-chlorobenzal diacetate,⁷ m. p. 56–57°, 2,6-dichlorobenzal diacetate,⁸ m. p. 90°, *m*-nitrobenzal diacetate,⁹ m. p. 68–69°, piperonal diacetate,⁶ m. p. 80°, cinnamal diacetate,¹⁰ m. p. 84–85°, crotonal diacetate,¹¹ b. p. 45–46° (14 mm.), and allylidene diacetate,¹¹ b. p. 81–82°, were prepared in good yield by mixing equivalent quantities of the appropriate aldehyde and acetic anhydride in the

(4) Coffin, *et al.*, *Can. J. Research*, **15B**, 229, 247, 254, 260 (1936); **18B**, 2213 (1940).

(5) Michael and Weiner, *THIS JOURNAL*, **58**, 680 (1936). These authors obtained an 81% yield of β -phenyl- β -propiolactone- α -carboxylic acid from benzaldehyde, malonic acid and a large excess of acetic anhydride in the presence of a trace of sulfuric acid. This material may also have been obtained in our experiment, but was not isolated.

(6) Knoevenagel, *Ann.*, **402**, 117 (1913).

(7) Shirlin, *J. Gen. Chem., U. S. S. R.*, **6**, 508–510 (1936), reports m. p. 51–53°, while Erdmann and Schwechten, *Ann.*, **260**, 57, 69 (1890), give m. p. 205–206°.

(8) Reich, *Bull. soc. chim.*, [4] **21**, 221 (1917), gives m. p. 85°.

(9) Van der Beck, *Rec. trav. chim.*, **47**, 309 (1938).

(10) Thiele and Meisenheimer, *Ann.*, **306**, 253 (1899).

(11) Wohl and Maag, *Ber.*, **43**, 3293 (1910).

(1) See German Patent 49,970 (1889), *Frdl.*, **2**, 50; Madsen, *Arch. Pharm.*, **245**, 45 (1907).

(2) Mowry, Yanko and Ringwald, *THIS JOURNAL*, **69**, 2358 (1947).

(3) An attempt to substitute benzaldehyde itself in this reaction confirmed the earlier reports of Madsen, reference 1, and deVarda, *Gazz. chim. ital.*, **21**, II, 348 (1891) that sulfuric acid-catalyzed reactions of this type result in nuclear alkylation with the formation of dibasic acids of the triphenylmethane series.

TABLE I

4-Keto-1,3-benzodioxane	Formula	Yield, %	B. p., °C.	Mm.	M. p., ^b °C.	Analyses, ^a %			
						Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
2-Methyl-	C ₉ H ₈ O ₃	87	97-98	1	33	.. ^c
2-Phenyl-	C ₁₄ H ₁₀ O ₃	83	60	74.4	74.6	4.46	4.63
2-(<i>o</i> -Chlorophenyl)-	C ₁₄ H ₉ O ₃ Cl	54	134	64.5	64.6	3.48	3.72
2-(2',6'-Dichlorophenyl)-	C ₁₄ H ₈ O ₃ Cl ₂	38	130	56.9	57.2	2.73	3.08
2-(<i>m</i> -Nitrophenyl)-	C ₁₄ H ₉ O ₃ N	52	141	62.2	62.4	3.34	3.51
2-(3',4'-Methylenedioxyphenyl)-	C ₁₆ H ₁₀ O ₅	48	118	66.7	66.9	3.74	3.94
2-Furyl-	C ₁₂ H ₈ O ₄	5	90	66.7	66.2	3.73	4.13
2-Styryl-	C ₁₆ H ₁₂ O ₃	66	99	76.2	76.2	4.80	4.82
2-Propenyl-	C ₁₁ H ₁₀ O ₃	24	150-155	10	76	69.5	69.5	5.31	5.37
2-Vinyl-	C ₁₀ H ₈ O ₃	5	110	2	33 ^d	68.3	68.3	4.58	4.67
2-(3',4'-Methylenedioxyphenyl)- 8-methyl-	C ₁₆ H ₁₂ O ₅	79	119	67.7	67.7	4.20	4.42
4-Keto-1,3-benzothioxane									
2-Phenyl-	C ₁₄ H ₁₀ O ₂ S	74	90	69.4	69.4	4.17	4.43
2-(3',4'-Methylenedioxyphenyl)-	C ₁₆ H ₁₀ O ₄ S	59	129	62.9	63.0	3.53	3.73

^a Microanalyses by the Arlington Laboratories, Fairfax, Va. ^b Uncorrected. ^c Mowry, Yanko and Ringwald, reference 2. ^d Mixed m. p. with 2-methyl-4-keto-1,3-benzodioxane, 15-18°.

presence of a trace of sulfuric acid, followed by neutralization with sodium acetate and distillation or recrystallization. For the preparation of furfural diacetate, m. p. 52-53°, it was preferable to use a trace of stannous chloride¹² at -10°.

Salicylic Acid-Aldehyde Diacetate Reactions.—The preparation of 2-phenyl-4-keto-1,3-benzodioxane is typical of these reactions.

A mixture of 104 g. of salicylic acid (0.75 mole), 151 g. (0.75 mole) of benzal diacetate, and a solution of 0.2 cc. of sulfuric acid in 50 cc. of glacial acetic acid was placed in a 500-cc. flask. A 50-cm. Vigreux column was attached and the system evacuated to 20-30 mm. pressure and heated with a bath at 70°. Acetic acid distilled out of the reaction as formed and the temperature of the bath was raised to 105° during a period of two hours. At the end of this time 133 g. of acetic acid had been removed. The product was dissolved in ether, washed with dilute solutions of sodium carbonate and sodium bisulfite. The ether was evaporated giving 141 g. (83%) of crude 2-phenyl-4-keto-1,3-benzodioxane, m. p. 55-58°. Two recrystallizations from dilute ethanol gave 120 g., m. p. 60°. With ferric chloride solution the product did not give the violet color characteristic of salicylic acid esters.

The other diacetates reacted in a similar fashion and the results are reported in Table I. In the case of ethylidene diacetate, acrolein diacetate and crotonal diacetate, after the theoretical amount of acetic acid had been liberated, the pressure was lowered to 3-5 mm. and the product distilled rapidly. The crude distillate was then recrystallized from dilute ethanol. In the case of allylidene diacetate, a large quantity of white solid crystallized from the reaction mixture while acetic acid was being removed. In one run the reaction was interrupted at this point, the material was dissolved in ether, and washed with sodium carbonate solution. The aqueous washings were acidified to precipitate a 52% yield of acetyl salicylic acid, which melted at 128-129° after recrystallization from dilute ethanol. The melting point was not depressed by mixture with an authentic sample, and the identity of this by-product was confirmed by analysis.

(12) Gilman and Wright, *Rec. trav. chim.*, **50**, 833 (1931).

Anal. Calcd. for C₉H₈O₄: C, 60.2; H, 4.57. Found: C, 60.43; H, 4.82.

Malonic Acid-Benzal Diacetate Reaction.—Malonic acid (78 g., 0.75 mole), benzal diacetate (151 g., 0.75 mole) and 0.2 cc. of concentrated sulfuric acid in 20 cc. of acetic acid were heated as described above. A nearly theoretical quantity (82 g.) of acetic acid was removed in two hours. The resultant solid was dissolved in dioxane and poured into excess cold aqueous sodium carbonate solution. The resultant precipitate, 12 g. (5%) was recrystallized from a dioxane-ethanol mixture to a constant melting point of 141-142°. It was assigned the structure of the cyclic ester, benzylidene benzalmalonate on the basis of analysis and analogy with the work of Michael and Weiner.⁵

Anal. Calcd. for C₁₇H₁₂O₄: C, 72.9; H, 4.33. Found: C, 72.6; H, 4.52.

The aqueous solution was acidified with hydrochloric acid and extracted with ether. Evaporation of the ether and aqueous solutions gave the same product, crude benzalmalonate in 37% yield. The melting point of the recrystallized product, 192-194° was not depressed by an authentic sample.

Summary

Salicylic acid will react with ethylidene diacetate to give 2-methyl-4-keto-1,3-benzodioxane in good yield. The diacetates of aromatic or α,β -unsaturated aldehydes have been shown to react satisfactorily to give 4-keto-1,3-benzodioxanes substituted in the 2-position, while the diacetates of other lower aliphatic saturated aldehydes and of chloral and furfural did not give the desired product. Thiosalicylic acid gives the analogous 4-keto-1,3-benzothioxanes. The method was not suitable for the preparation of cyclic esters of malonic acid.

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