AN IMPROVED SYNTHESIS OF ACETOSYRINGONE[1]

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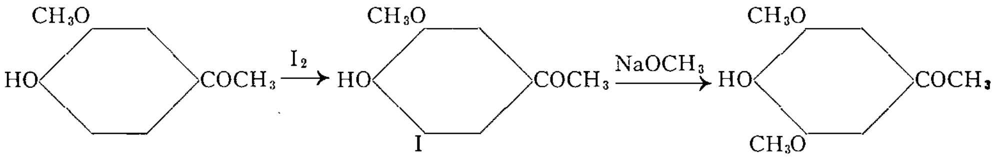
ABSTRACT

Acetosyringone has been synthesized from acetovanillone, in better than a 50% yield, through conversion to 5-iodoacetovanillone followed by its interaction with sodium methoxide in the presence of copper catalyst. The previously unreported intermediate, 5-iodoacetovanillone, was characterized by methylation to 5-iodoacetoveratrone and subsequent oxidation to the known 5-iodoveratric acid.

One of the more fruitful fields of research on the chemical structure of lignin has been that of oxidation (3). By means of the alkaline nitrobenzene oxidation of wood meal itself, or of isolated lignins, good yields of the phenolic aldehydes vanillin and syringaldehyde have been obtained, along with lesser amounts of acetovanillone* (4-hydroxy-3-methoxyphenyl methyl ketone) (I) and acetosyringone* (4-hydroxy-3,5-dimethoxyphenyl methyl ketone) (III). With respect to the structure of lignin the latter two derivatives, being C_6—C—C fragments, are of more structural significance than the former more highly degraded C_6—C derivatives. In order to study the problems associated with the separation of these four lignin derivatives from admixture, it was necessary to have available pure samples of each compound. Vanillin and acetovanillone are available commercially and syringaldehyde may be synthesized by any of several methods (1, 11, 10, 13), but the reported syntheses of acetosyringone have been difficult and have resulted in poor over-all yields. The present work describes an improved two-stage synthesis of acetosyringone from acetovanillone.

Synthetic acetosyringone was reported first by Bradley and Robinson (2), who used a multistep synthesis starting from O-benzylsyringoyl chloride and ethyl acetoacetate, and who reported that their product melted at 117°C. Later, Mauthner (8) described the more direct synthesis involving the aluminum chloride catalyzed rearrangement of 2,6-dimethoxyphenyl acetate. Leger and Hibbert (7) and later Pepper and Hibbert (12) used this method of Mauthner and prepared acetosyringone melting at 120.5–121.5°C. and 121–122°C. and in yields of 11 and 12.6% respectively. A new synthesis has been effected starting from acetovanillone (I) according to the following equations:



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[1] *Manuscript received June 25, 1956.*

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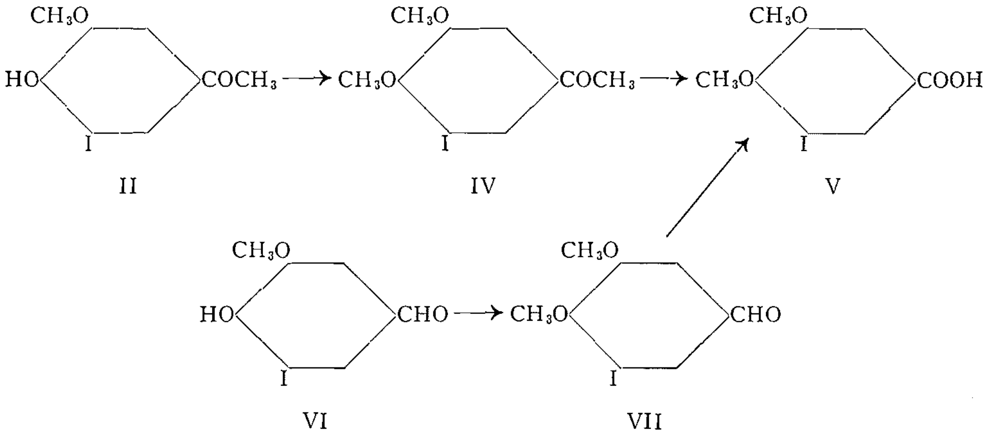
**The names acetovanillone and acetosyringone and those of their corresponding derivatives are used extensively in the literature and hence are used throughout this paper.*

The procedure of Carles (4) for the iodination of vanillin, involving the addition of a methanolic solution of iodine to a warmed aqueous solution of vanillin, was applied to the iodination of acetovanillone, and a product obtained in 5.6% yield, after recrystallization from acetic acid, m.p. 175–177°C. A modification of the procedure used by Erdtman (5) for the synthesis of 5-iodovanillin, whereby the sodium hydroxide was replaced by sodium carbonate, gave rise to an iodinated derivative, in 82.5% yield, m.p. 172–174°C. No depression of melting points was found in admixture of samples of the iodinated products made by the two methods.

Since 5-iodoacetovanillone was previously unreported, it was first necessary to prove the structure of the iodinated product. The position of the ring-substituted iodine could be proved if the unknown were oxidized to a product identical with an authentic sample of 5-iodovanillic acid. All attempts to isolate 5-iodovanillic acid from the alkaline liquors of either sodium hypoiodite or sodium hypobromite oxidations were unsuccessful. Fuson and Bull (6) have reported that haloform reactions on either hydroxy- or nitro-acetophenones do not result in formation of the expected acids even though the haloform itself may be formed. Attempts to oxidize 5-iodovanillin by the method of Pearl (9), using silver oxide, were also unsuccessful.

The following series of reactions served to characterize the unknown as 5-iodoacetovanillone.



The unknown was converted by methylation to 5-iodoveratryl methyl ketone (IV) and hence to 5-iodoveratric acid (V) by oxidation with potassium permanganate. This last compound was identical with a sample of the acid prepared by the methylation of 5-iodovanillin (VI) to 5-iodoveratraldehyde (VII) followed by oxidation.

The 5-iodoacetovanillone was then converted to acetosyringone (III) by a procedure similar to that whereby 5-iodovanillin had been converted to syringaldehyde (13), i.e. by the interaction with methanolic sodium methoxide at elevated temperatures in the presence of copper catalyst. The crude acetosyringone was purified by recrystallization from water. The results of six such experiments are given in Table I.

TABLE I

REACTION OF 5-IODOACETOVANILLONE WITH SODIUM METHOXIDE USING COPPER CATALYST

Run	Temp., °C.	Time, hr.	MeOH-sol.,* gm.	Acetosyringone			
				From water		From mother liquor	
				Wt., gm.	M.p., °C.	Wt., gm.	M.p., °C.
1	149–151	1	8.0	4.1	116–123	1.5	60–90
2	141–144	1	8.8	4.9	113–120	1.8	65–110
3	133–135	1	10.0	4.1	110–121	—	—
4	135	†	6.0	1.5	115–120	2.2	98–105
5	136–139	0.5	8.2	2.7	115–121	3.2	98–110
6	135–137	4.75	10.0	4.0	119–122	1.0	119–123

**Theoretical yield of acetosyringone, 9.4 gm.*

†*Reaction mixture heated to 135°C., then cooled immediately.*

EXPERIMENTAL

All melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected.

Synthesis of 5-Iodoacetovanillone

(*a*) Acetovanillone (5.1 gm.) was dissolved in water (100 ml.) and a solution of iodine (3.0 gm.) in methanol (100 gm.) was added. The mixture was well stirred and maintained at a temperature of 50°C. for 24 hr. After the mixture was cooled, the resultant precipitate was removed by filtration and was recrystallized from acetic acid, to yield a product (0.5 gm., 5.6%), m.p. 175–177°C.

(*b*) Acetovanillone (50 gm.) and sodium bicarbonate (16.0 gm.) were dissolved, with warming, in water (300 ml.). To this a solution of iodine (75.6 gm.) dissolved in a solution of potassium iodide (85.0 gm.) in water (400 ml.) was added slowly with stirring whilst the temperature was maintained at 80°C. After the addition of approximately 25% of the iodine solution a yellow precipitate appeared. After complete addition, the resultant solution was decolorized with a minimum quantity of sodium thiosulphate and filtered while hot. After the precipitate collected, it was washed with water (500 ml.) and dried; yield 72.5 gm., 82.5%, m.p. 172–174°C. After recrystallization of the precipitate from ethanol–water, then ethanol, the melting point was 178–179°C. Calc. for $C_9H_9O_3I$: C, 37.00; H, 3.11%. Found: C, 37.02; H, 3.11%. The *p*-nitrophenylhydrazone melted at 212–213°C. A mixed melting point with the sample prepared by Carles' method gave no depression.

Characterization of 5-Iodoacetovanillone. 5-Iodoveratraldehyde

5-Iodovanillin (3 gm.) and sodium bicarbonate (20 gm.) were heated in water (100 ml.) to 55°C. Dimethyl sulphate (6.7 gm.) was added dropwise during one half hour, the temperature being maintained at 55°C. On cooling, the mixture was extracted with ether (100 ml.), and the ether extract washed with *N* sodium hydroxide, dried, and concentrated to yield white crystals; yeild 1.24 gm., m.p. 70–72°C.; reported m.p. 72–73°C. (14).

5-Iodoveratric acid from 5-iodoveratraldehyde.—5-Iodoveratraldehyde (1.24 gm.) was added to pyridine (6 ml.) and the mixture maintained at 55°C. during the slow addition of potassium permanganate (5%, 8 ml.). After removal of the precipitated manganese dioxide, the filtrate was discolored with a little sodium bisulphite, poured into water, and acidified with concentrated hydrochloric acid. The crude product that precipitated (0.67 gm., 51%), m.p. 179–180°C., was purified by reprecipitation, by acidification, from an ether-extracted alkaline solution; m.p. 183–183.5°C.; reported m.p. 184–185°C. (13).

5-Iodoacetoveratrone.—A solution of 5-iodoacetovanillone (1.2 gm.), dimethyl sulphate (2.7 gm.), and ethanol (7 ml.) was heated to reflux. Sodium hydroxide (10 *N*, 3 ml.) was added dropwise over a period of 15 min. After the further addition of dimethyl sulphate (2.7 gm.), sodium hydroxide (10 *N*, 3 ml.), the mixture was refluxed for one-half hour and poured into water (200 ml.). The alkaline solution was extracted with ether (2 × 50 ml.); the extract, after drying and concentration, yielded crude 5-iodoacetoveratrone, 1.0 gm. (79%), m.p. 73–77°C. Recrystallization from ethanol–water, then ethanol, gave white crystals, m.p. 78–79°C. Calc. for $C_{10}H_{11}O_3I$: C, 39.23; H, 3.62%. Found: C, 39.17; H, 3.64%. No previous report on this compound could be found.

5-Iodoveratric acid from 5-iodoacetoveratrone.—5-Iodoacetoveratrone (1.0 gm.) was dissolved in pyridine (10 ml.) and the mixture heated to 60°C. during the addition of potassium permanganate (5%, 30 ml.) in 5 ml. portions. After removal of the manganese dioxide, the filtrate was discolored with sodium bisulphite, made alkaline with sodium hydroxide, and extracted with ether. The aqueous layer, after acidification, was extracted with ether (100 ml.). From this extract, after drying and concentration, 5-iodoveratric acid was obtained (0.33 gm., 33%), m.p. 183–184°C. A mixed melting point determination on samples of the acid made by both methods showed no depression.

Acetosyringone

A typical synthesis is as follows: Sodium (12 gm.) was dissolved in anhydrous methanol (300 ml.) and this solution together with copper powder (B.D.H. precipitated, 7.7 gm.) and 5-iodoacetovanillone (14 gm.) was heated, with shaking, in a bomb, capacity 1410 ml., of an Aminco high pressure hydrogenator, Model No. 406-01DA. Temperature control was ±4°C. At the end of the specified reaction time the bomb was cooled and the contents rinsed into a beaker with water (600 ml.) The copper catalyst was removed by filtration and the filtrate acidified with concentrated hydrochloric acid. This precipitated any unchanged 5-iodoacetovanillone, which was much less soluble, *ca.* 1/200, than the required acetosyringone. The filtrate was extracted with chloroform (6 × 200 ml.) and the extract was then washed with 5% sodium thiosulphate (100 ml.), then with water (2 × 100 ml.), and finally evaporated under reduced pressure to dryness. The residue was extracted with methanol (100 ml.) whereby some red colored impurities were separated as a methanol-insoluble portion. Evaporation of the methanol gave the crude acetosyringone, which was crystallized from water. A sample recrystallized from water, then Skellysolve "C", melted at 123–124°C.; reported m.p. 121–122°C. (12). Calc. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17%. Found: C, 61.40; H, 6.14%. The *p*-nitrophenylhydrazone melted at 193.5–194.5°C.; reported m.p. 194.5–195.5°C. (7).

ACKNOWLEDGMENTS

The authors wish to thank the Saskatchewan Research Council for financial assistance and also the Salvo Chemical Corporation, Rothschild, Wisconsin, for their kind donation of the acetovanillone.

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