THE SYNTHESIS OF AROYL METHYL KETONES AS LIGNIN MODEL SUBSTANCES

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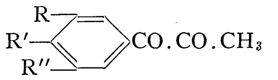
ABSTRACT

A series of aroyl methyl ketones ($ArCOCOCH_3$ in which Ar was phenyl, *p*-hydroxyphenyl, *p*-methoxyphenyl, 4-hydroxy-3-methoxyphenyl, 3,4-dimethoxyphenyl, 4-hydroxy-3,5-dimethoxyphenyl, and 3,4,5-trimethoxyphenyl) has been prepared by the oxidation, using selenium dioxide, of the correspondingly substituted benzyl methyl ketones.

INTRODUCTION

Two diketones, vanilloyl methyl ketone (IV) and syringoyl methyl ketone (VI), have been isolated from the products obtained by the acid-catalyzed solvolysis of wood or isolated lignins (1, 2). The characterization of such derivatives has contributed to the present knowledge of the chemical structure of lignin. They serve, too, as interesting model substances for lignin research. The reported syntheses of IV by Brickman, Hawkins, and Hibbert (3) and of VI by Kulka, Hawkins, and Hibbert (4) involve many steps and low overall yields. An investigation was made to find a more suitable mode of synthesis of such aroyl methyl ketones in order that a sufficient amount might be obtained for an extended study of their properties and chemical reactions.



I R = R′ = R″ = H
II R = R″ = H, R′ = HO
III R = R″ = H, R′ = CH_3O
IV R = CH_3O, R′ = HO, R″ = H
V R = R′ = CH_3O, R″ = H
VI R = R″ = CH_3O, R′ = HO
VII R = R′ = R″ = CH_3O

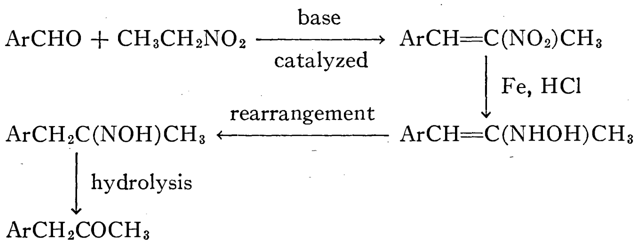
The method that was investigated involved the synthesis of ketones of the formulae $ArCOCH_2CH_3$ and $ArCH_2COCH_3$ and their subsequent oxidation, using selenium dioxide, to the corresponding α-diketones. The latter route was shown to be preferable and compounds IV and VI were obtained with little difficulty. The method was then extended to include the synthesis of five other related diketones (I, II, III, V, VII), only one of which (I) had been made previously by this method.

RESULTS AND DISCUSSION

Initially, monoketones of the formula $ArCOCH_2CH_3$ were prepared by the silver oxide oxidation of the corresponding alcohols, $ArCH(OH)CH_2CH_3$, which had been synthesized from the aryl aldehyde and ethyl magnesium bromide. Following the method of Roberti, York, and MacGregor (5), the required 1-(4-hydroxy-3-methoxyphenyl)-1-propanol was prepared in 68% yield. Similarly, but using tetrahydrofuran instead of diethyl ether, syringaldehyde was converted to 1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanol in 52% yield. Both compounds gave the characteristic color reaction with quinone monochloroimide which is indicative of a *p*-hydroxybenzyl alcoholic group (6, 7).

The oxidation of the alcohol to the corresponding keto compound using silver oxide had been shown by Pearl (8) to proceed readily in the case of 1-(4-hydroxy-3-methoxyphenyl)-1-propanol in 89% yield. Initially some difficulty was experienced in repeating these results, especially in crystallization of the syrupy product. This was overcome partly by increasing the reaction time from 1½ hours to 5 hours and using freshly generated sulphur dioxide. Under these conditions, the highly viscous product solidified slowly and could be recrystallized from petroleum ether to yield the required ketone (propiovanillone) in 50.5% yield. 1-(4-Hydroxy-3,5-dimethoxyphenyl)-1-propanone (propiosyringone) was prepared by the same method. This product solidified readily and could be recrystallized to give the required ketone in 40.3% yield. Subsequently it was found that the synthesis and oxidation of monoketones of the formula $ArCH_2COCH_3$ gave better yields of the required α-diketones and attention was directed, therefore, to the synthesis using this route.

The synthesis of monoketones of the formula, $ArCH_2COCH_3$, was based on the procedure reported by Kulka and Hibbert (9) and outlined as follows:



$$\begin{tikzcd}
ArCHO + CH_3CH_2NO_2 \arrow[r, "base", "catalyzed"'] & ArCH{=}C(NO_2)CH_3 \arrow[d, "{Fe, HCl}"] \\
ArCH_2C(NOH)CH_3 \arrow[d, "hydrolysis"] & ArCH{=}C(NHOH)CH_3 \arrow[l, "rearrangement"'] \\
ArCH_2COCH_3 &
\end{tikzcd}$$

No difficulty was encountered in the condensation of vanillin with nitroethane using the methylamine hydrochloride – sodium carbonate method, but the similar reaction using syringaldehyde gave yields of product which varied widely from run to run. A more successful condensation was achieved using the method reported by Kaufmann (10) in which the methylamine hydrochloride was replaced by aqueous ethylamine. The condensation of other substituted benzaldehydes was then effected using one or other of these methods. The yields of the resulting 1-aryl-2-nitro-1-propenes are given in Table I.

TABLE I

Percentage yields of $ArCH{=}C(NO_2)CH_3$

Aldehyde	Methylamine method (9)	Ethylamine method (10)
p-Hydroxybenzaldehyde	49	65
Anisaldehyde	—	76
Vanillin	72	—
Veratraldehyde	—	76
Syringaldehyde	52	56
3,4,5-Trimethoxybenzaldehyde	66	52

The conversion of the 1-aryl-2-nitro-1-propenes to the substituted benzyl methyl ketones offered no difficulty. Purification of the monoketones was effected through the formation of the sodium bisulphite addition product. The yields are given in Table II.

It had been reported by Wegmann and Dahn (11) that benzyl methyl ketone could be oxidized, using selenium dioxide in dioxane, to the corresponding benzoyl methyl ketone. Since it was found possible to readily duplicate these results, attention was directed to this method as a means of synthesis of the required α-diketones from the correspondingly

TABLE II

Percentage yields of $ArCH_2COCH_3$ and $ArCOCOCH_3$

Ar—	$ArCH{=}C(NO_2)CH_3$ to $ArCH_2COCH_3$	$ArCH_2COCH_3$ to $ArCOCOCH_3$
Phenyl		60
p-Hydroxyphenyl	66	44
p-Methoxyphenyl	73	33
4-Hydroxy-3-methoxyphenyl	78	32
3,4-Dimethoxyphenyl	76	34
4-Hydroxy-3,5-dimethoxyphenyl	63	11
3,4,5-Trimethoxyphenyl	89	38

substituted benzyl methyl ketones. The conversion of 4-hydroxy-3-methoxybenzyl methyl ketone to 4-hydroxy-3-methoxybenzoyl methyl ketone was chosen as a typical system with which to study the optimum conditions for oxidation and the most satisfactory procedure for the isolation and purification of the product.

Using, initially, the conditions reported by Wegmann and Dahn (11), the oxidation was carried out for 4 hours in dioxane at reflux temperature. The resulting crude reaction product was studied by gas–liquid chromatography using a 6-ft, 1/4-in., 15% Apiezon N on Fluoropak column at 220° C. Three well-separated peaks, with retention times of 4.0, 5.5, and 6.8 minutes, indicated the presence of three compounds in this product. By comparison with authentic samples the peaks were shown to correspond to vanillin, unchanged 4-hydroxy-3-methoxybenzyl methyl ketone, and the required vanilloyl methyl ketone* respectively. Since approximately 65% of the eluted material was the α-diketone, this method of synthesis warranted a more detailed investigation to determine the optimum conditions for a maximum yield of vanilloyl methyl ketone.

An equimolar ratio of selenium dioxide to the monoketone was adopted and a study made of the effect of varying the time of oxidation, at reflux temperatures, and the nature of the solvent system. Reaction times of 4, 8, 12, 18, and 24 hours gave rise to the diketone in yields which represented percentage relative abundances of 32, 46, 64, 64, and 64 respectively. Having, therefore, chosen 12 hours as the most suitable reaction time, a similar study was made of the effect of the solvent system. For dimethyl sulphoxide, dioxane, tetrahydrofuran, acetic acid, acetic anhydride, and ethanol the percentage relative abundances were 75, 65, 53, 36, a trace, and zero respectively. For simplicity, dioxane was chosen as the solvent system for all subsequent oxidations.

Two separate methods of isolation and purification of the required vanilloyl methyl ketone were investigated. In the first instance, a study was made of the separation of the nickel glyoxime salt and its subsequent decomposition with dilute sulphuric acid to liberate the free diketone (4). The second method involved a column chromatographic separation of the crude oxidation product and was found to be more successful. Silica gel was used as the column packing and petroleum ether (b.p. 40–60°) followed by petroleum ether containing 5% diethyl ether, effected the elution of the vanilloyl methyl ketone. Using these conditions of oxidation and isolation, seven substituted benzyl methyl ketones were oxidized successfully to the corresponding α-diketones. The yields are given in Table II.

On hydrolysis of the precipitated nickel glyoxime salt of vanilloyl methyl ketone, a white precipitate separated. This compound was characterized as vanillic acid. Further

The donation of an authentic sample of vanilloyl methyl ketone by Dr. J. A. F. Gardner, Superintendent, Forest Products Laboratory, Vancouver, B.C., was much appreciated.

tests showed that the vanillic acid did not arise as a product of this hydrolysis or by oxidation of any vanillin that may have been present but rather that it was produced directly by oxidation of either the 4-hydroxy-3-methoxybenzyl methyl ketone or the vanilloyl methyl ketone. In subsequent syntheses involving the oxidation of *p*-methoxybenzyl methyl ketone and of 3,4,5-trimethoxybenzyl methyl ketone the two corresponding acids, anisic acid and 3,4,5-trimethoxybenzoic acid, were isolated and characterized. The mechanism of formation of these acids was not determined. A closer examination of a probable oxidation by air or peroxides in the dioxane must be made before a benzyl–acyl bond cleavage can be attributed to the action of selenium dioxide under these conditions.

The electronic absorption spectrum of each of the substituted benzoyl methyl ketones was determined using ethanol as the solvent. Table III records the λ_{max} and log ϵ_{max} for each diketone. The reported spectral bands of benzil and diacetyl are included for comparison.

TABLE III

Electronic absorption spectra of $ArCOCOCH_3$

Ar =	λ_{max}	log ϵ_{max}
1. Phenyl	255	4.36
2. *p*-Hydroxyphenyl	296	4.06
	225	3.82
3. *p*-Methoxyphenyl	294	4.00
	223	3.81
4. 4-Hydroxy-3-methoxyphenyl	320	4.93
	291 (sh)	—
	235	4.86
5. 3,4-Dimethoxyphenyl	317	3.64
	284 (sh)	3.50
	235	3.55
6. 4-Hydroxy-3,5-dimethoxyphenyl	326	4.02
7. 3,4,5-Trimethoxyphenyl	295	3.74
Benzil (ArCOCOAr)	259	4.31
	370	1.89
Diacetyl ($CH_3COCOCH_3$)	435	1.30

The spectral data recorded in Table III are in general agreement with the theory regarding the effect of ring substituents on the absorption spectra of aromatic compounds.

EXPERIMENTAL

All melting points are uncorrected. Ultraviolet spectra were measured using a Cary Model 14 spectrometer. Infrared spectra were determined using a Perkin–Elmer Model 21 spectrometer with sodium chloride optics. Gas–liquid chromatography was performed using a Beckman GC-2 chromatograph with a thermal conductivity detector unit. This machine had been modified by placing the injection system as close as possible to one end of the column and by modifying it to make it more comparable electronically to the GC-2A.

Synthesis of 1-Aryl-1-propanones

(i) 1-(4-Hydroxy-3-methoxyphenyl)-1-propanone

1-(4-Hydroxy-3-methoxyphenyl)-1-propanol was prepared according to the method of Roberti, York, and MacGregor (5) and then oxidized, using silver oxide, to 1-(4-hydroxy-3-methoxyphenyl)-1-propanone as described by Pearl (8). For the latter step it was found necessary to increase the time of reflux to 5 hours and to use freshly prepared sulphur dioxide otherwise no crystalline product was obtained. Under the modified conditions, the crude oily product solidified on standing and was recrystallized from petroleum ether (30–60°) to yield colorless needle-shaped crystals, m.p. 59–60; reported m.p. 61–62 (8). Calc. for $C_{10}H_{12}O_3$: OCH_3, 17.22%. Found: OCH_3, 17.10%.

(ii) 1-(4-Hydroxy-3,5-dimethoxyphenyl)-1-propanone

Synthesis of 1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanol.—Syringaldehyde (10 g) was dissolved in dry tetrahydrofuran (150 ml) and the solution treated with another solution of ethyl magnesium bromide (prepared from ethyl bromide (42 g) and magnesium (10 g)). The resulting oily product crystallized on standing, yield 6.1 g (52.3%). Recrystallization from benzene gave white crystals, m.p. 94–95°; reported m.p. 98° (12). Calc. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.61; OCH_3, 29.3%. Found: C, 62.40; H, 7.48; OCH_3, 29.0%.

Oxidation of 1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanol.—1-(4-Hydroxy-3,5-dimethoxyphenyl)-1-propanol (3.0 g) was treated with sodium hydroxide (7 g) and silver nitrate (8 g) and a similar procedure followed to that used for the oxidation of 1-(4-hydroxy-3-methoxyphenyl)-1-propanol. The yield of crude product was 1.2 g (40.3%). Recrystallization from aqueous ethanol gave white crystals, m.p. 108–109°; reported m.p. 109–110° (4).

Synthesis of 1-Aryl-2-propanones

2-Nitro-1-aryl-1-propenes

The experimental details are given for the preparation of a typical compound. Other compounds of the same series but differing in the ring substituent pattern were prepared by a similar procedure. The necessary data for each such individual synthesis are recorded in Table IV.

(i) Using the method of Kulka and Hibbert (9).—Vanillin (6 g) was dissolved in ethanol (10 ml) and to the solution, nitroethane (3 ml), methylamine hydrochloride (0.2 g), and sodium carbonate (0.016 g) were added. After 2 days at room temperature in the dark, the reaction mixture was cooled to 0°, the yellow needle-like crystals removed by filtration, washed with dilute sulphuric acid and with water, and dried. The yield was 5.9 g (71.5%). After recrystallization from a mixture of ethanol and ether the 2-nitro-1-(4-hydroxy-3-methoxyphenyl)-1-propene melted at 101–102°; reported m.p. 101–102° (9).

In Table IV are the experimental data for the similar condensations of *p*-hydroxybenzaldehyde, syringaldehyde, and 3,4,5-trimethoxybenzaldehyde.

(ii) Using the method of Kaufmann (10).—Veratraldehyde (15 g) was added to nitroethane (8 ml) and 20 drops of aqueous (75%) ethylamine added to the mixture. An initial turbidity slowly disappeared and a yellow oil separated which crystallized on standing. After 8 days, the crystals were removed by filtration and dried. The yield was 15.2 g (75.5%). After recrystallization from ethanol the 2-nitro-1-(3,4-dimethoxyphenyl)-1-propene melted at 73° (10).

In Table IV are the experimental data for the similar condensations of syringaldehyde, *p*-hydroxybenzaldehyde, and anisaldehyde.

1-Aryl-2-propanones

The experimental details are given for the preparation of a typical compound. All other compounds were prepared by a similar procedure, the necessary data for which are recorded in Table V.

(i) Using the method of Kulka and Hibbert (9).—2-Nitro-1-(4-hydroxy-3-methoxyphenyl)-1-propene (20 g) was dissolved in hot ethanol (200 ml) and hot water (500 ml), iron powder (40 g), ferric chloride (1.6 g), and concentrated hydrochloric acid added. The reaction mixture was refluxed, with stirring, for 6 hours and then concentrated to half the volume by removal of ethanol. The precipitated black iron oxide was filtered and washed with hot water. The combined filtrate and washings were extracted with benzene. From this extract was obtained an oil which was distilled to yield a clear, yellow product of 1-(4-hydroxy-3-methoxyphenyl)-2-propanone (13.4 g) (77.7%), b.p. 125° at 0.45 mm; reported b.p. 115° at 0.15 mm (9).

In Table V are the experimental data for the similar reduction and subsequent hydrolysis of the five other 2-nitro-1-aryl-1-propenes.

Synthesis of Aroyl Methyl Ketones

Vanilloyl Methyl Ketone

Selenium dioxide (2.4 g, 0.02 mole) was dissolved in dioxane (12 ml) and water (2 ml). 1-(4-Hydroxy-3-methoxyphenyl)-2-propanone (3 g, 0.02 mole) was added and the mixture refluxed for 12 hours. Initially the reaction mixture became red in color but gradually metallic selenium precipitated as a black powder. The selenium was removed by filtration and the dioxane and water removed by distillation. The residue, a dark brown tarry material, was distilled to give a clear yellow oil weighing 2.1 g, b.p. 115° at 0.6 mm. This product only partially crystallized.

(i) Purification of vanilloyl methyl ketone via the nickel glyoxime salt method.—From 3 g of the crude reaction product, prepared as above, the nickel glyoxime salt of the α-diketone was precipitated according to the method of Kulka, Hawkins, and Hibbert (4). The yield was 1.32 g. To hydrolyze this salt, it was added to 12 *N* sulphuric acid (400 ml), and the mixture was allowed to stand at room temperature for 24 hours and then at 40° for 4 hours. During hydrolysis a white precipitate separated (see below) which was removed by filtration. The filtrate was extracted with benzene in a continuous liquid–liquid extractor, the extract dried over anhydrous sodium sulphate and sodium bicarbonate, and concentrated to remove the excess benzene. A further slight precipitation of the white solid occurred during the concentration and it was removed by filtration. The residual oil was purified by fractional crystallization from benzene to give vanilloyl methyl ketone (0.55 g, 7%), m.p. 65–69°; reported m.p. 70–71° (9).

The white solid that precipitated during the hydrolysis was recrystallized from aqueous ethanol and characterized as vanillic acid on the basis of the following evidence: m.p. 204°, reported m.p. 207°; no melting

TABLE IV

The preparation of 2-nitro-1-aryl-1-propenes

Aldehyde	Aldehyde, g	Ethanol, ml	$C_2H_5NO_2$, ml	CH_3NH_3Cl, g	Na_2CO_3, g	$C_2H_5NH_2$ (75%), drops	2-Nitro-1-aryl-1-propene g	Yield, %	M.p., °C	Reported m.p., °C
p-Hydroxybenzaldehyde	5	15	3.0	0.2	0.015		3.6	49	128–129	*
Vanillin	6	10	3.0	0.2	0.016		5.9	72	101–102	101–102 (9)
Syringaldehyde	9	25	4.5	0.3	0.024		6.1	52	101–102	103–104 (9)
3,4,5-Trimethoxybenzaldehyde	2	10	1.0	0.1	0.020		1.7	66	95–96	95 (13)
p-Hydroxybenzaldehyde	5	15	3.0			9	4.8	65	128–129	
Anisaldehyde	15	10	7.5			15	16.2	76	42–43	†
Veratraldehyde	15		8.0			20	15.2	76	73	73 (10)
Syringaldehyde	5	10	3.0			8	3.7	56	102–103	103–104 (9)

*Fine, needle-shaped orange crystals, recrystallized from methanol–water.

†Calc. for $C_{10}H_{11}O_3N$: C, 62.16; H, 5.74%. Found: C, 61.80; H, 5.88%.

TABLE V

The preparation of 1-aryl-2-propanones

$ArCH{=}C(NO_2)CH_3$ Ar =	Weight, g	Ethanol	Water	Fe powder	12*N* HCl	$FeCl_3$	1-Aryl-2-propanone			
		ml	ml	g	ml	g	g	Yield, %	Found	Reported
p-Hydroxyphenyl	4	50	150	10	5	0.4	2.2	66	b.p. 140° at 0.08 mm	m.p. 35° (14)
p-Methoxyphenyl	10	150	350	20	10	0.8	6.2	73	b.p. 110° at 0.2 mm	b.p. 150° at 20 mm (15)
4-Hydroxy-3-methoxyphenyl	20	200	500	40	20	1.6	13.4	78	b.p. 125° at 0.45 mm	b.p. 115° at 0.15 mm (9)
3,4-Dimethoxyphenyl	10	150	350	20	10	0.8	6.6	76	b.p. 122° at 0.6 mm	b.p. 118° at 0.2 mm (16)
4-Hydroxy-3,5-dimethoxyphenyl	4.7	50	150	10	5	0.32	2.6	63	m.p. 67–68°	m.p. 68–69° (9)
3,4,5-Trimethoxyphenyl	2.8	25	120	5	2.5	0.06	2.2	89	m.p. 66–67°	*

*Recrystallized from diethyl ether to give white crystals. Calc. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19%. Found: C, 64.03; H, 7.35%.

TABLE VI

The preparation of aroyl methyl ketones

$ArCH_2COCH_3$, Ar =	Weight, g	Selenium dioxide, g	Dioxane:water, ml:ml	Aroyl methyl ketones			
				g	Yield, %	Found	Reported
Phenyl	20	16	100:20	13.1	60	b.p. 110° at 10 mm	b.p. 102° at 12 mm (11)
p-Hydroxyphenyl	3.5	2.5	15:3	1.5	44	m.p. 92–93°	m.p. 92–93.5° (17)
p-Methoxyphenyl	3.5	2.3	15:3	1.2	33	m.p. 44–45°	m.p. 46° (18)
4-Hydroxy-3-methoxyphenyl	2.0	1.1	10:2	0.7	32	m.p. 70–71°	m.p. 70–71° (3)
3,4-Dimethoxyphenyl	3.0	1.6	15:3	1.1	34	m.p. 67–68°	m.p. 69–70° (16)
4-Hydroxy-3,5-dimethoxyphenyl	2.0	0.9	10:3	0.25	11.4	m.p. 78–79°	m.p. 80–81° (4)
3,4,5-Trimethoxyphenyl	3.0	1.4	15:3	1.2	37.6	m.p. 65–66°	*

*Recrystallized from petroleum ether as yellow crystals. Calc. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92%. Found: C, 60.51; H, 6.01%.

point depression with an authentic sample; identical infrared spectrum with that of an authentic sample; and by analysis. Calc. for $C_8H_8O_4$: C, 57.1; H, 4.76; OCH_3, 18.4%. Found: C, 57.13; H, 4.92; OCH_3, 18.27%.

(ii) Purification of vanilloyl methyl ketone via the column chromatography method.—A chromatographic column (2 in.×30 in.) was half filled with dry petroleum ether (b.p. 40–60°) and silica gel (200 g) was added slowly with constant stirring. During this addition the petroleum ether was slowly drawn off from the bottom and the loss replaced through the top. When an air-bubble-free, well-packed column was obtained, the petroleum ether was drawn off until a 0.5-cm layer of solvent remained above the column packing. The crude oxidation product (2.0 g) was dissolved in a minimum amount of diethyl ether and placed on the top of the column. Elution with petroleum ether (40–60°) resulted in the slow separation of a yellow band. After the passage of 2 liters of the eluant, the band had moved one-third the length of the column. At this stage 5% diethyl ether was added to petroleum ether and 1.5 liters of this mixed solvent eluted the band completely. Evaporation of the solvent left yellow crystals of vanilloyl methyl ketone (0.92 g, 33%). After recrystallization from ethanol–water the melting point was 70–71°; reported m.p. 70–71° (9). The quinoxaline derivative melted at 160–161°; reported m.p. 162–163° (3).

In a similar manner six other aroyl methyl ketones were synthesized and isolated. The experimental data are given in Table VI.

ACKNOWLEDGMENT

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