

Attempts to Synthesize α -(3,4-Dimethoxyphenyl)- glycerol Derivatives

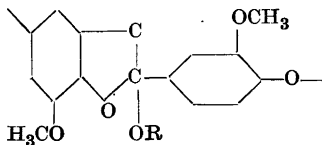
BENGT O. LINDGREN

*Organisk-kemiska Institutionen, and Institutionen för Cellulosesteknik och Träkemi,
Kungliga Tekniska Högskolan, Stockholm, Sweden*

Holmberg showed that α -phenethyl alcohol reacts with sulphite cooking acid with formation of a sulphonic acid¹. From this and other evidence² he concludes that the sulphonation of lignin is due to the substitution of sulphonic acid groups for hydroxyl groups of benzyl alcohol type.

In a recent paper, Erdtman, Lindgren, and Pettersson³ showed that in the later phases of the sulphonation of lignin, the reaction involves the substitution of sulphonic acid groups for hydroxyl groups. Setting out from these results, the writer examined vanillyl alcohol, veratryl alcohol, and their homologues⁴. These benzyl alcohols were found to be suitable model substances for the sulphonation and condensation of lignin.

Poly-ethers containing benzyl alcohol groups were prepared by Erdtman and Leopold⁵ and found to behave like lignin in their reactions with sulphite solutions. Erdtman⁶, however, considers that there are in lignin two different groups which are responsible for the sulphonation. Only the most reactive of these groups is assumed to be of benzyl alcohol type, the other being a cyclic acetal group of the type

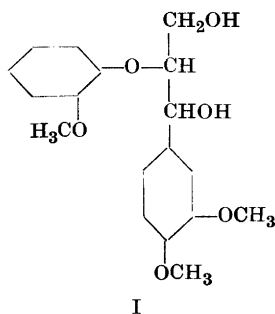


in which R represents a carbohydrate or lignin residue.

Enkvist and Moilanen⁷ recently showed that vanillyl alcohol is also a good model substance for certain reactions of lignin during the sulphate digestion.

In the discussions of the structure of lignin, phenyl glycerol derivatives play an important rôle^{2,8}. For this reason, the experiments (see Scheme 1)

which are described in this paper were initiated. The synthesis of α -(3,4-dimethoxyphenyl)-glycerol derivatives, particularly the guaiacyl ether I, was attempted. Although the synthesis of these compounds from 1-(3,4-dimethoxyphenyl)-propanone(-1) derivatives could not be accomplished, a series of interesting reactions were encountered.

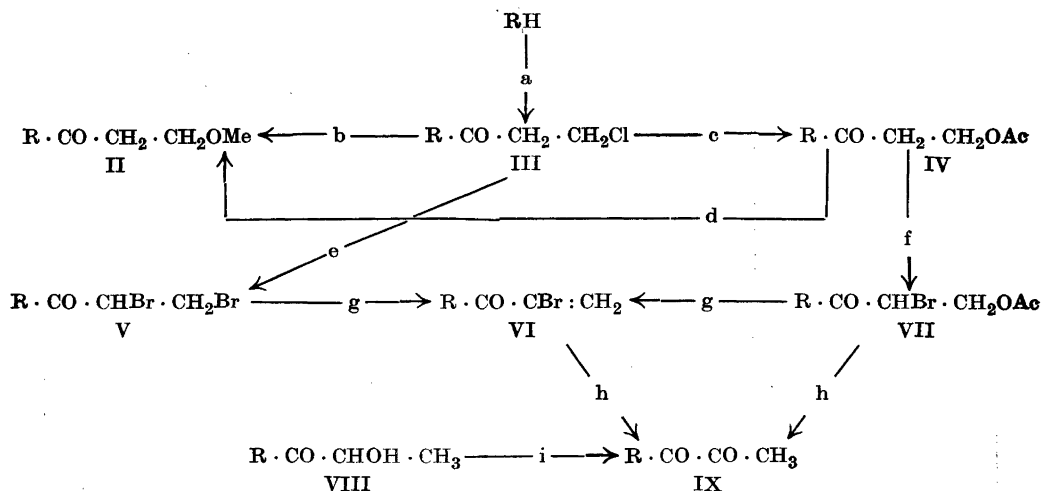


3-Acetoxy-1-(3,4-dimethoxyphenyl)-propanone(-1) (IV, see Scheme 1), synthesized according to the method of West, Hawkins, and Hibbert⁹, was brominated to form 3-acetoxy-2-bromo-1-(3,4-dimethoxyphenyl)-propanone(-1) (VII). Several attempts were made to substitute acetoxy or 2-methoxyphenoxy group for the bromine atom of the latter compound (VII). In all cases, however, the only substances obtained were the elimination products. When heated with potassium acetate in acetic acid, the bromo acetoxy compound VII yielded 1-(3,4-dimethoxyphenyl)-propandione(-1,2) (IX). On heating with guaiacol and a base, compound VII yielded 2-bromo-1-(3,4-dimethoxyphenyl)-propene(-2)-one(-1) (VI) and (or) the diketone IX.

The bromine atom in the 3 position of 2,3-dibromo-1-(3,4-dimethoxyphenyl)-propanone(-1) (V) is also easily eliminated. With guaiacol and potassium carbonate, in acetone solution, the substance yields the unsaturated bromo compound VI.

The transformation of the bromo acetoxy compound VII into the diketone IX belongs to a type of reaction of which only a few examples have been described in the literature. The formation of a diketone has been observed by Bradley and Eaton¹² in the case of 3-chloro-1-acetoxy-1-phenyl-propanone(-2) (X Scheme 2), mild hydrolysis of the latter yielding 1-phenyl-propandione(-1,2) (XV). Gardner and Hibbert¹³ showed that similar compounds, such as 3-chloro-1-acetoxy-1-(3-methoxy-4-acetoxy-phenyl)-propanone(-2) (XI) and 1,3-diacetoxy-1-(3-methoxy-4-acetoxy-phenyl)-propanone(-2) (XII), are converted by the action of mild hydrolytic agents into the diketone XVI. The formation of such diketones is of interest in lignin chemistry since Hibbert and co-

Scheme 1. Schematic diagram of the synthesis*.



* Except the synthesis of 2-hydroxy-2-ethoxy-1-(3,4-dimethoxyphenyl)-ethanone(-1).

R = 3,4-dimethoxyphenyl-

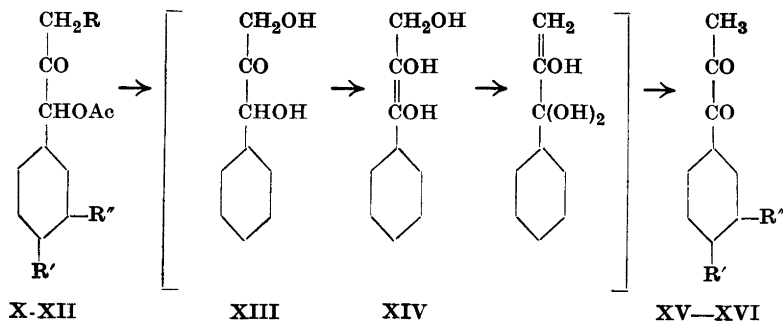
a) Friedel-Crafts synthesis, according to Freudenberg and Fikentscher¹⁰. b) Potassium hydroxide in methanol. c) Potassium acetate in acetic acid according to Hibbert and co-workers⁹. d) Potassium hydroxide in methanol according to Hibbert and co-workers⁹. e) Bromine in acetic acid. f) Bromine in chloroform. g) Potassium carbonate with acetone. h) Potassium acetate in acetic acid. i) Copper sulphate in pyridine according to Hibbert and co-workers¹¹.

workers have isolated the diketone XVI from the ethanolysis products of wood¹⁴.

Gardner and Hibbert¹³ concluded that the diketone XVI "is formed as the result of an allyl shift in a dismutation ene-diol product XIV arising from the hydrolysis intermediate, 1,3-dihydroxy-1-(4-hydroxy-3-methoxy-phenyl)-propanone(-2)" (XIII). The transformation of the bromo acetoxy compound VII into the diketone IX by potassium acetate in acetic acid, however, does not necessarily involve a molecular rearrangement. The diketone IX may be formed via the unsaturated bromo compound VI, since this compound forms the diketone IX under the same conditions.

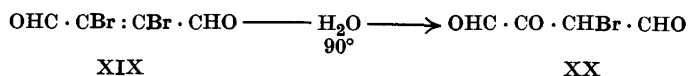
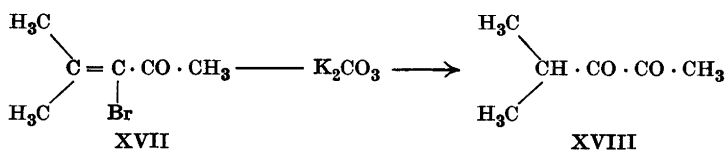
In general, there is a pronounced diminution in reactivity of a halogen atom adjacent to a double bond. The bromine atom of the unsaturated bromo compound VI, however, is very reactive. As mentioned above, it reacts with potassium acetate in acetic acid to yield the diketone IX. The high reactivity

Scheme 2. The formation of diketones.



	R	R'	R''
X	Cl	H	H
XI	Cl	OAc	OMe
XII	OAc	OAc	OMe

	R'	R''
XV	H	H
XVI	OH	OMe



of a halogen atom in a similar position has been observed by Pauly and Lieck¹⁵ in the case of bromo mesityl oxide (XVII Scheme 2) on heating with potassium carbonate this compound yielded the diketone XVIII. One of the bromine atoms of dibromo maleinic aldehyde (XIX) is also easily substituted. On heating with water at 90°, it yields the compound XX¹⁶.

Attempts were made to synthesize the diketone IX by the oxidation of propioveratrone with selenium dioxide in dioxane or acetic acid solution. In no case was the diketone IX obtained. On the other hand, acetoveratrone is readily oxidized into 3,4-dimethoxyphenyl glyoxal by selenium dioxide in dioxane solution in the manner used by Fodor and Kovács¹⁷ to synthesize several other, substituted phenyl glyoxals. 3,4-Dimethoxyphenyl glyoxal is transformed into a semiacetal, 2-hydroxy-2-ethoxy-1-(3,4-dimethoxyphenyl)-ethanone(-1), by heating with ethanol.

EXPERIMENTAL

3-Methoxy-1-(3,4-dimethoxyphenyl)propanone(-1) (II)

3-Chloro-1-(3,4-dimethoxyphenyl)propanone(-1)¹⁰ (III) (8.6 g) was mixed with hot methanol (50 ml). Methanolic potassium hydroxide solution (77 ml, 0.488N) was added and the mixture was boiled for about one minute. After filtration and neutralization, the filtrate was evaporated to dryness in a vacuum. Recrystallization from ligroin yielded a substance, which had a m. p. of 69° (5.5 g, yield 65 %). The m. p. was increased to 71° by further recrystallizations. The substance gave no m. p. depression with the compound II (m. p. 71°), prepared according to West, Hawkins, and Hibbert⁹.

3-Acetoxy-2-bromo-1-(3,4-dimethoxyphenyl)propanone(-1) (VII)

3-Acetoxy-1-(3,4-dimethoxyphenyl)propanone(-1)⁹ (IV) (10 g) was dissolved in chloroform (50 ml), containing a drop of concentrated hydrochloric acid. Bromine (6.7 g) dissolved in chloroform (40 ml) was slowly added at room temperature. The reaction was started by means of ultra-violet irradiation. The red solution obtained was shaken with sodium bicarbonate solution and with water. After drying over anhydrous sodium sulphate the solution was filtered through a column of aluminium oxide. By this operation the colour of the solution was changed to pale brown. After evaporating the solution in a vacuum, the residue crystallized. Recrystallization from isopropyl ether yielded a substance which had a m. p. of 87–91° (7.6 g, yield 58 %). Further recrystallizations increased the m. p. to 94–95°.

$C_{11}H_9O_3Br(OCH_3)_2$	Calc.	OCH_3	18.7
	Found	»	18.8

2,3-Dibromo-1-(3,4-dimethoxyphenyl)propanone(-1) (V)

3-Chloro-1-(3,4-dimethoxyphenyl)propanone(-1)¹⁰ (III) (4 g) was dissolved in acetic acid (30 ml), containing a drop of concentrated hydrochloric acid. Bromine (2.8 g), dissolved in acetic acid (15 ml), was slowly added at room temperature. The reaction was started by means of ultra-violet irradiation. The solution was left over-night and then evaporated in a vacuum desiccator over sodium hydroxide. The residue crystallized and the crystals were washed with methanol (4.95 g, yield 80 %, calculated on the assumption that the product were the pure dibromo compound). Recrystallizations from methanol yielded a product which had the m. p. of 74°–78°.

$C_9H_6OBr_2(OCH_3)_2$	Calc.	Br	45.4
	Found	Halogen (determ. by titr. and calc. as Br)	46.8
	Calc.	OCH_3	17.6
	Found	»	18.4

The ratio halogen/ OCH_3 is 1.01.

The product is evidently contaminated with the chloro derivative.

2-Bromo-1-(3,4-dimethoxyphenyl)propanone(-2)-one(-1) (VI)

1. 2,3-Dibromo-1-(3,4-dimethoxyphenyl)propanone(-1) (V) (2 g) was dissolved in acetone (20 ml). The solution was refluxed on a steam bath for one hour with anhydrous

potassium carbonate (2 g). The solution was then filtered and evaporated. The crystalline residue (1.2 g) was recrystallized from ethyl acetate. The substance obtained (0.6 g, yield 40 %) melted at 121–122°.

$C_9H_5OBr(OCH_3)_2$	Calc.	OCH ₃	22.9	Br	29.5
	Found	»	22.6	»	29.9

2. From 3-acetoxy-2-bromo-1-(3,4-dimethoxyphenyl)-propanone(-1) (VII) the unsaturated bromo compound VI was similarly obtained. The yield was about 70 %.

1-(3,4-Dimethoxyphenyl)-propanone(-1,2) (IX)

1. 3-Acetoxy-2-bromo-1-(3,4-dimethoxyphenyl)-propanone(-1) (VII) (6.5 g) was heated with anhydrous potassium acetate (11.4 g) and acetic acid (30 ml) for 6 hours on a steam bath. Water was then added. After keeping for a few days in a refrigerator a yellow substance crystallized. The crystals were removed by filtration. By extraction of the mother liquor with chloroform, further amounts of the compound were obtained. Recrystallizations from ligroin yielded a product which had a m. p. of 69.5–70.5° (1.5 g, total yield 37 %). The compound contained 29.6 % methoxyl. The diketone IX requires 29.8 % methoxyl.

The compound gave no m. p. depression with the diketone IX (m. p. 71°), prepared by oxidation of 2-hydroxy-1-(3,4-dimethoxyphenyl)-propanone(-1) (VIII) with copper sulphate in pyridine¹¹, nor did the quinoxaline derivatives of these two samples give any depression in a mixed m. p. determination.

2. 2-Bromo-1-(3,4-dimethoxyphenyl)-propene(-2)-one(-1) (VI), treated in the same manner as the bromo acetoxy compound VII, gave the diketone IX in 80 % yield.

The quinoxaline derivative of 1-(3,4-dimethoxyphenyl)-propanone(-1,2) (IX)

The diketone IX and *o*-phenyldiamine were dissolved in alcohol-water (1:1) and heated to boiling for about one minute. On cooking the quinoxaline derivative crystallized. Recrystallization from methanol yielded a substance which had a m. p. of 117°.

$C_{15}H_{10}N_2(OCH_3)_2$	Calc.	OCH ₃	22.1
	Found	»	21.8

Attempts to couple 3-acetoxy-2-bromo-1-(3,4-dimethoxyphenyl)-propanone(-1) (VII) with guaiacol

A mixture of the bromo acetoxy compound VII, a suitable base, guaiacol (x moles per a mole of VII, compare Table 1), and a solvent (only in the experiments 1 and 4) was heated on a steam bath for 2 hours with stirring.

The reaction mixture was diluted with water and extracted with chloroform or benzene (the latter solvent was used in those cases when the amount of bromide ion in the aqueous solution was to be determined). The extracted aqueous solution was acidified with nitric acid, and the bromide ion was precipitated with silver nitrate. The products recovered from the chloroform extract were examined in various ways.

Table 1 shows the yields of the substances obtained in these experiments.

In a substitution reaction bromide ion would of course be formed. Since the bromine atom of the unsaturated bromo compound is reactive, bromide ion could also be formed by hydrolysis of VI. For this reason the yield of bromide ion gives only a maximum value of the substitution.

In the experiments 2 and 3 no appreciable amounts of the substitution product, 3-acetoxy-2-(2-methoxy-phenoxy)-1-(3,4-dimethoxyphenyl)-propanone(-1), could be formed, as the yields of bromide ion were so low.

In experiment 4, on the other hand, the yield of bromide ion was high. By filtering a benzene solution of the reaction product through a column of aluminium oxide and evaporating the benzene, a yellow oil was obtained. The oil was dissolved in aqueous methanol and titrated against sodium hydroxide with phenolphthalein. The equivalent weight was 189 (that of the diketone IX is 208). By boiling a methanol solution of the oil and *o*-phenyldiamine for one minute, a precipitate of the quinoxaline derivative of the diketone IX was formed. Hence the oil was evidently impure diketone IX. Judging from the equivalent weight, the yield of the diketone IX was 45 %.

Table 1. The yields of the reaction products from coupling experiments with the bromo acetoxy compound VII and guaiacol.

Expt.	Moles of guaiacol per a mole of VII	Solvent	Base	The yields of %		
				Br ⁻	VI	IX
1	1	acetone	K ₂ CO ₃		70	
2	53	no solv.	K ₂ CO ₃	14		
3	53	» »	KOAc	17		
4	10	dioxane	MgO	76		45

Attempt to couple 2,3-dibromo-1-(3,4-dimethoxyphenyl)-propanone(-1) (V) with guaiacol

The bromo compound V was treated in the same manner as the bromo acetoxy compound VII in experiment 1 above. The only substance obtained was the unsaturated bromo compound VI. The yield was 40 %.

2-Hydroxy-2-ethoxy-1-(3,4-dimethoxyphenyl)-ethanone(-1)

Acetoveratrone (10 g) and selenium dioxide (11 g) were dissolved in dioxane (50 ml) containing water (2 ml). The reaction mixture was boiled for 4 hours on a steam bath. The separated selenium was filtered off, and the yellow solution evaporated in a vacuum at 40°. The residue was treated with water (75 ml) on a steam bath for 3 hours with constant stirring, and the resulting solution decolorized with charcoal, filtered, and concentrated to a small volume. The residue, a yellow oil, was dissolved in hot ethanol. On cooling, white crystals were obtained (7.4 g, yield 56 %, m. p. 60–64°). Recrystallization from ethanol yielded a product which had a m. p. of 69–71° (3.4 g, yield 25 %).

C ₁₂ H ₁₆ O ₅	Calc. alkoxy (as OCH ₃)	38.7	C	59.9	H	6.66
	Found	» » »		» 59.8	»	» 6.61

The quinoxaline derivative of 1-(3,4-dimethoxyphenyl)-ethandione(-1,2)

2-Hydroxy-2-ethoxy-1-(3,4-dimethoxyphenyl)-ethanone(-1) (0.5 g) was dissolved in water-ethanol (1 : 1, 10 ml). *o*-Phenyldiamine (0.5 g) was added and the solution boiled for a few minutes. On cooling, a crystalline product was obtained. Recrystallization from methanol yielded a substance, which had a m. p. of 120–121°.

$C_{16}H_{14}O_2N_2$	Calc.	N	10.5
	Found	»	10.4

SUMMARY

1. The following new substances have been synthesized (see Scheme 1): 2,3-dibromo-1-(3,4-dimethoxyphenyl)-propanone(-1), 3-acetoxy-2-bromo-1-(3,4-dimethoxyphenyl)-propanone(-1), 2-bromo-1-(3,4-dimethoxyphenyl)-propene(-2)-one(-1), and 2-hydroxy-2-ethoxy-1-(3,4-dimethoxyphenyl)-ethanone(-1).

1-(3,4-Dimethoxyphenyl)-propandione(-1,2) and 1-(3,4-dimethoxyphenyl)-ethandione(-1,2) have been characterized as quinoxaline derivatives.

2. Attempts have been made to synthesize 2,3-dihydroxy-1-(3,4-dimethoxyphenyl)-propanone(-1) derivatives. They have, however, failed.

3. The bromine atom of 2-bromo-1-(3,4-dimethoxyphenyl)-propene(-2)-one(-1) is shown to react readily with mild hydrolytic agents with formation of 1-(3,4-dimethoxyphenyl)-propandione(-1,2).

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REFERENCES

- Hedén, S., and Holmberg, B. *Svensk Kem. Tid.* **48** (1936) 207.
- Holmberg, B. *Finska Kemistsamfundets Medd.* **54** (1945) 124.
- Erdtman, H., Lindgren, B. O., and Pettersson, T. *Acta Chem. Scand.* **4** (1950) 228.
- Lindgren, B. O. *Acta Chem. Scand.* **1** (1947) 779; **3** (1949) 1011.
- Erdtman, H., and Leopold, B. *Acta Chem. Scand.* **2** (1948) 535; **3** (1949) 1358.
- Erdtman, H. *Research* **3** (1950) 63.
- Enkvist, T., and Moilanen, M. *Svensk Papperstidn.* **52** (1949) 183.
- Freudenberg, K. *Fortschritte der Chemie organischer Naturstoffe.* II. Wien (1939) p. 8.
- West, K. A., Hawkins, W. L., and Hibbert, H. *J. Am. Chem. Soc.* **63** (1941) 3035.
- Freudenberg, K., and Fikentscher, H. *Ann.* **440** (1924) 36.
- Eastham, A. H., Fischer, H. E., Kulka, M., and Hibbert, H. *J. Am. Chem. Soc.* **66** (1944) 26.
- Bradley, W., and Eaton, J. K. *J. Chem. Soc.* **1937** 1913.
- Gardner, J. A. F., and Hibbert, H. *J. Am. Chem. Soc.* **66** (1944) 607.

14. Pyle, J. J., Brickman, L., and Hibbert, H. *J. Am. Chem. Soc.* **61** (1939) 2198; Brickman, L., Pyle, J. J., Hawkins, W. L., and Hibbert, H. *Ibid.* **62** (1940) 986; Brickman, L., Hawkins, W. L., and Hibbert, H. *Ibid.* **62** (1940) 2149.
15. Pauly, H., and Lieck, H. *Ber.* **33** (1900) 501.
16. Chavanne, G. *Compt. rend.* **153** (1911) 187; *Bull. soc. chim. Belges* **25** (1911) 273.
17. Fodor, G., and Kovács, Ö. *J. Am. Chem. Soc.* **71** (1949) 1045.

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