ACTA CHEMICA SCANDINAVICA 7 (1953) 561–569

Synthesis and Reactions of α-(3-Methoxy-4-hydroxyphenyl)-glycerol ("Guaiacylglycerol"). I. Preliminary Experiments

E. ADLER and K. J. BJÖRKQVIST

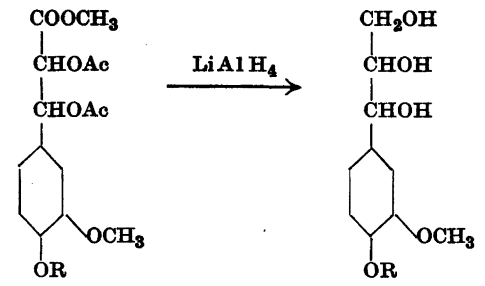
Department of Wood Chemistry, Swedish Forest Products Research Laboratory, Stockholm, Sweden

Recently, Adler and Björkqvist [1] reported the synthesis of α-(3,4-dimethoxyphenyl)-glycerol ("veratrylglycerol") (II) by lithium aluminium hydride reduction of the methyl ether of α,β-diacetoxyhydroferulic acid methyl ester (I). The behaviour of veratrylglycerol, especially on heating with sulphite solutions and with ethanolic hydrochloric acid proved to be of considerable interest in connection with the chemistry of lignin [2].

Simultaneously, attempts have been made to prepare the hitherto unknown phenolic compound, α-(3-methoxy-4-hydroxyphenyl)-glycerol ("guaiacylglycerol") (IV). This compound could be expected to be prepared by lithium aluminium hydride reduction of α,β-diacetoxy-acetylhydroferulic acid methyl ester (III). The preparation of this substance and its conversion into guaiacylglycerol are described in the following paper [3].

The present communication deals with some preliminary experiments in this field. They resulted in two different procedures for the preparation of methyl α-bromo-β-acetoxy-acetylhydroferulate (XVIII), which can be further converted, *via* III, into guaiacylglycerol [3]. Although both procedures are — due to the lower yields obtained — of less practical value for the present purpose than the procedure given in the following paper [3], they will be briefly reported as they involve some unexpected observations.

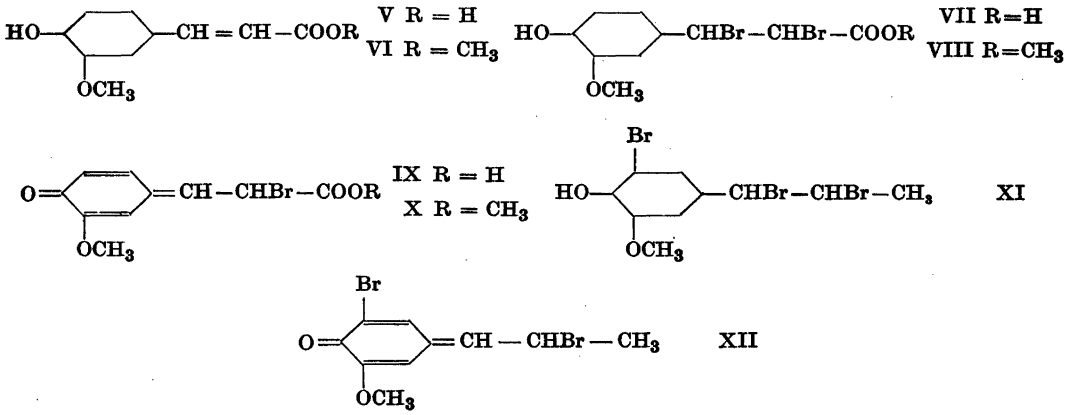
The α,β-dibromo-hydroferulic acid (VII) and its methyl ester (VIII) seemed to be suitable starting materials for the preparation of the triacetate III



I R = CH_3
III R = Ac

II R = CH_3
IV R = H

or the corresponding free carboxylic acid, or of similar products (with OH instead of one, two, or three OAc groups) which with lithium aluminium hydride could be expected to be converted into guaiacylglycerol (IV).



The dibromides VII and VIII were easily obtained from ferulic acid (V) and methyl ferulate (VI), respectively.

When the ether, chloroform, or benzene solutions of the dibromides VII or VIII were shaken with aqueous sodium bicarbonate (or acetate) they turned yellow, and this in analogy with the behaviour of other *p*-(and *o*-) hydroxybenzyl halides must be due to the formation of the "quinone methides" IX and X, respectively. In contrast with simple quinone methides, which rapidly undergo polymerization, "quinone ethides" and "propides" have previously been found to be comparatively stable. For instance, substance XII, which is obtained from XI, has been isolated by Zincke and Hahn [4] in a crystalline state. The yellow-coloured products obtained from VII and

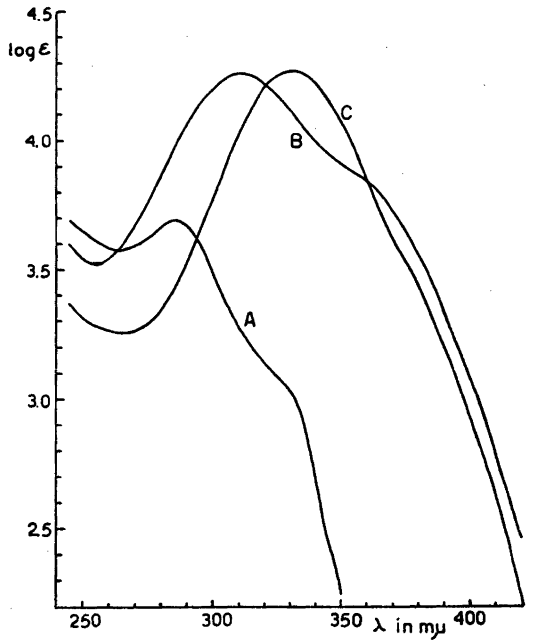


Fig. 1. Light absorption curves of A: α,β-Dibromohydroferulic acid methyl ester (VIII), B: Quinone methide X (based on the concentration of VIII), C: Quinone methide XII, in chloroform solutions.

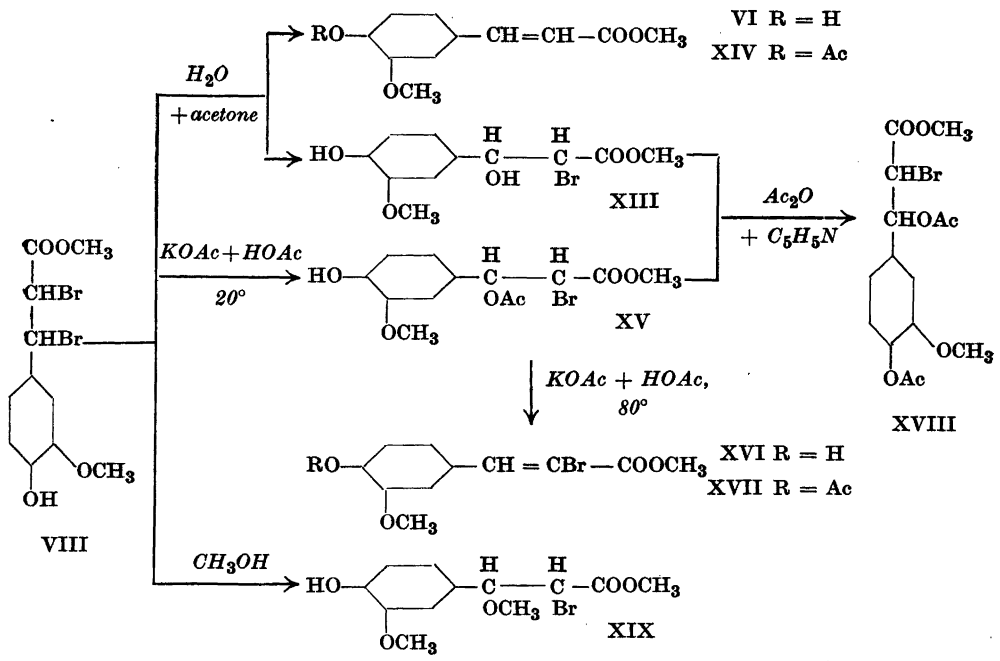
VIII are rather stable in the organic solvents mentioned above, but attempts to isolate the presumed quinone methides (IX, X) led only to amorphous, probably polymerized products.

Fig. 1 shows the absorption spectra of the dibromide VIII and of the yellow chloroform solution, presumably containing X, obtained from it on treatment with aqueous sodium bicarbonate. For comparison, the spectrum of the crystalline quinone methide XII has been included.

Further reactions of the dibromide VIII, characteristic of *p*-hydroxybenzyl halides, are presented in Scheme 1.

Treatment of VIII with aqueous acetone at room temperature produced the carbinol XIII. The yield of this substance, however, did not exceed 15 per cent, the bulk of the reaction product being an oil, from which after acetylation methyl acetylferulate (XIV) was isolated. The main reaction, therefore, consisted in debromination to methyl ferulate (VI), which is in agreement with previous observations made in similar cases (*cf.* [1,5]).

Scheme 1.



Attempts to replace the bromine atom in XIII by acetoxyl were unsuccessful. Treatment with potassium acetate (acetic acid solution, 2 h, 100°) yielded unchanged material, whereas only ill-defined oily products were obtained under more drastic conditions.

As could be expected, the bromine atom in the "benzyl" position in VIII could be replaced by acetoxyl under very mild conditions. The action of potassium acetate in cold acetic acid solution was sufficient to produce the acetate XV, although the yield of this substance was only slightly better than that of the carbinol XIII. Treatment of XV with potassium acetate in acetic acid at 80° did not result in the desired exchange of the second bromine atom, but yielded the unsaturated bromide XVI, which was purified as acetate (XVII). The structure of XVII is also supported by the fact that its ultraviolet absorption spectrum is very similar to that of methyl acetylferulate (XIV) (Fig. 2).

On acetylation (acetic anhydride-pyridine) the carbinol XIII and the mono-acetate XV yielded the same diacetate (XVIII), which can be further converted into the triacetate III [3]. Due to the low yields of XIII and XV, the over-all yield of XVIII, based on the dibromide VIII, was, however,

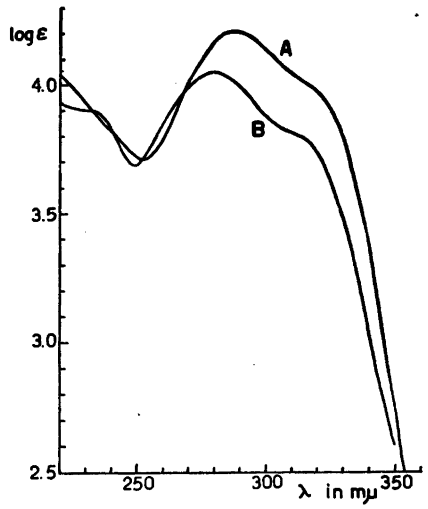


Fig. 2. Ultraviolet absorption curves of A: α-Bromo-acetylferulic acid methyl ester (XVII), B: Acetylferulic acid methyl ester (XIV), in 96 per cent ethanol.

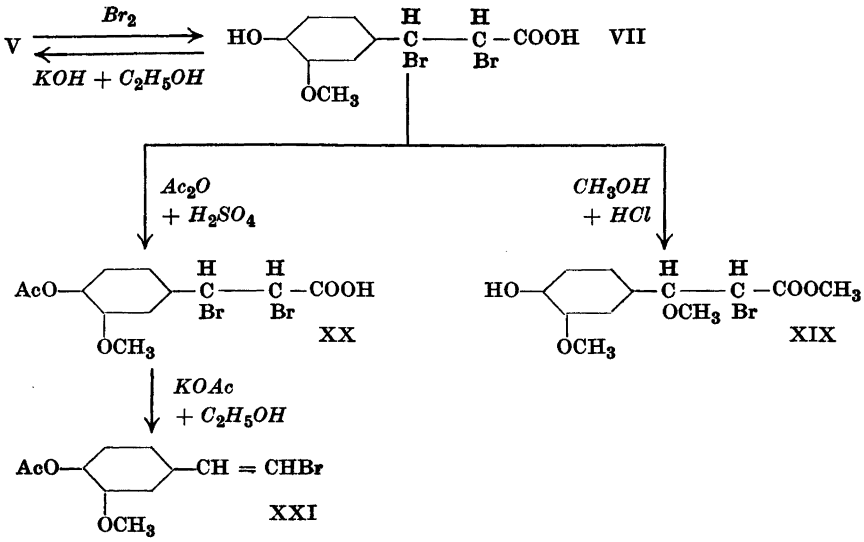
not satisfactory, and a better procedure for the preparation of XVIII (and III) will be given in the following communication [3].

In a "normal" hydroxybenzyl halide reaction, the dibromide VIII, when dissolved in cold methanol, was converted in good yield into the benzyl methyl-ether XIX.

The dibromide of the free ferulic acid (VII) could be expected to be less favourable than VIII as a starting material for the production of suitably hydroxylated or acetoxylated hydroferulic acids. It was already known that similar brominated *p*-hydroxy- or *p*-alkoxy cinnamic acids undergo complete debromination or lose hydrogen bromide and carbon dioxide yielding the corresponding ω-bromo-vinyl compounds when treated with aqueous acetone or with potassium acetate (*cf.*[1]). These reactions were therefore not investigated.

The action of ethanolic potassium hydroxide on the dibromide VII resulted in debromination, ferulic acid (V) being the only reaction product which could be isolated. An attempt was then made to stabilize the substituents of the side-chain by acetylating the phenolic hydroxyl group in VII. Due to the high reactivity of the bromine atom in "benzyl" position, pyridine could not be used as an acetylation catalyst; the acetate XX was, however, readily formed with acetic anhydride and very little concentrated sulphuric acid at room temperature. When treated with potassium acetate (in ethanol) the acetate

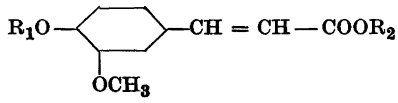
Scheme 2.



XX, however, lost hydrogen bromide and carbon dioxide and yielded the bromostyrene XXI (Scheme 2).

The normal formation of the methyl ether XIX (*cf.* also Scheme 1) by the action of methanol and dry hydrogen chloride on VII may also be noted.

As shown in Scheme 2, ferulic acid (V) was first brominated and the dibromide (VII) obtained was then acetylated. It may be of interest to mention that this sequence of reactions could not be reversed. Surprisingly enough it was found that acetylferulic acid (XXII), in chloroform or acetic acid solutions, does not consume bromine. Similarly, it proved impossible to brominate the methyl ester of acetylferulic acid (XIV), whereas methyl ferulate (VI) is readily brominated.



XXII R_1 = Ac, R_2 = H
XIV R_1 = Ac, R_2 = CH_3

XXIII R_1 = CH_3, R_2 = H
XXIV R_1 = CH_3, R_2 = CH_3

Contrary to acetylation, methylation of the phenolic hydroxyl group in ferulic acid or methyl ferulate, however, does not affect the reactivity of the double bond, both ferulic acid methyl ether (XXIII)[6] and the corresponding

ester (XXIV)[1] being smoothly brominated. Isoeugenol acetate also adds bromine very readily, and hence, in XXII and XIV, the inertness of the double bond towards bromine seems to be the result of the combined influences of the *p*-acetoxyl and the carboxyl (carbomethoxyl) groups.

EXPERIMENTAL

α,β-Dibromo-hydroferulic acid (VII). A solution of 32 g of bromine (0.2 mole) in 250 ml acetic acid was added dropwise to a solution of 38.8 g of ferulic acid (V) (0.2 mole) in 250 ml of the same solvent. The temperature was kept below 10°. The colourless crystalline substance which precipitated in nearly quantitative yield was filtered off and dried in a desiccator over potassium hydroxide. After recrystallization from ethylacetate-hexane it formed needles, m.p. 158—159° (decomposition). (Found: C 34.0; H 2.82; Br 44.6. Calc. for $C_{10}H_{10}O_4Br_2$ (354.0): C 33.9; H 2.85; Br 45.1.)

α,β-Dibromo-hydroferulic acid methyl ester (VIII). Bromine (77 g) was added during five minutes to an ice-cooled, slowly stirred solution of methyl ferulate (VI) (100 g) (prepared from ferulic acid [7] with methanol-hydrogen chloride, m.p. 63—64° [8]) in chloroform (250 ml). After the bromine was added, the dibromide crystallized out, was filtered off and washed with a chloroform-hexane mixture. Recrystallization from ethylacetate-hexane and benzene-hexane yielded needles of m.p. 133—134° (decomposition). Yield 76 %. (Found: C 35.6; H 3.23; Br 43.2; OCH_3 16.8. Calc. for $C_{11}H_{12}O_4Br_2$ (368.1): C 35.9; H 3.29; Br 43.4; OCH_3 16.9.)

α-Bromo-β-hydroxyhydroferulic acid methyl ester (XIII). Water (30 ml) was added to a solution of α,β-dibromohydroferulic acid methyl ester (36.8 g) in acetone or dioxan (200 ml). The solution acquired a yellow colour (quinone methide?), which disappeared within a few minutes. After 3 hours the solution was evaporated under reduced pressure. The oily residue was dissolved in chloroform and the solution was dried (Na_2SO_4) and concentrated under reduced pressure. The crystalline material obtained on addition of hexane was recrystallized from chloroform and from benzene. Prisms, m.p. 118—119°; yield about 15 %. (Found: C 43.3; H 4.38; Br 25.6; OCH_3 20.1. Calc. for $C_{11}H_{13}O_5Br$ (305.1): C 43.3; H 4.29; Br 26.2; OCH_3 20.3.)

Acetylation with acetic anhydride in pyridine at room temperature yielded α-bromo-β-acetoxy-acetylhydroferulic acid methyl ester (XVIII), m.p. 100—101°, no depression with a sample obtained according to the procedure given in the following paper [3].

Methyl acetylferulate (XIV). The oily residue obtained from the mother liquor of XIII, when treated with acetic anhydride and pyridine at room temperature, yielded a considerable quantity of acetylferulic acid methyl ester (XIV), m.p. 122—123°, undepressed on admixture of a sample of the substance prepared by acetylation of methylferulate. (According to Pacsu and Stieber [9], who prepared substance XIV by methylation of acetylferulic acid with diazomethane, the m.p. is 124°.) (Found: C 62.6 H 5.73; OCH_3 25.0. Calc. for $C_{13}H_{14}O_5$ (250.2): C 62.4; H 5.64; OCH_3 24.8.)

α-Bromo-β-acetoxyhydroferulic acid methyl ester (XV). Anhydrous potassium acetate (10 g = 0.1 mole) dissolved in acetic acid (150 ml) was added to a solution of the dibromide VIII (36.8 g = 0.1 mole) in acetic acid (150 ml). After 24 hours at room temperature, potassium bromide was filtered off, and the solution was evaporated under reduced pressure. The oily residue was dissolved in benzene, and the benzene solution was washed with water, dried (Na_2SO_4) and diluted with hexane. The semi-crystalline

material which precipitated was recrystallized from benzene-hexane and from benzene yielding prisms, m.p. 113—114°. Yield 15—20 %. (Found: C 45.0; H 4.29; Br 22.7; OCH_3 17.9. Calc. for $C_{13}H_{15}O_6Br$ (347.2): C 45.0; H 4.36; Br 23.0; OCH_3 17.9.)

Acetylation with acetic anhydride in pyridine solution at room temperature yielded XVIII, m.p. 100°, no depression with samples obtained from XIII or according to the procedure described in the following paper [3].

α-Bromo-acetylferulic acid methyl ester (XVII). A solution of 6.0 g of XV and 1.75 g of potassium acetate in 100 ml of acetic acid was heated at 80° for 10 hours, then concentrated under reduced pressure and diluted with water. The oil which separated was extracted with benzene, and the benzene solution was washed with water, dried over anhydrous sodium sulphate, and concentrated. On the addition of hexane a crystalline substance of m.p. 72—79° (impure substance XVI) was obtained. Acetylation with acetic anhydride and pyridine at room temperature yielded thin plates (recrystallized from 80 per cent methanol and abs. ethanol), m.p. 96—97° (XVII). (Found: C 47.6; H 3.87; Br 24.4; OCH_3 18.9. Calc. for $C_{13}H_{13}O_5Br$ (329.2): C 47.4; H 3.98; Br 24.3; OCH_3 18.9.)

α-Bromo-β-methoxy-hydroferulic acid methyl ester (XIX). 1. A solution of 15 g α,β-dibromohydroferulic acid methyl ester (VIII) in 100 ml of methanol was set aside overnight at room temperature, then neutralized with excess calcium carbonate, filtered, diluted with water and extracted with chloroform. The chloroform solution was dried over sodium sulphate and concentrated to about 25 ml. On addition of hexane the methyl ether separated, and after recrystallization from methanol-water formed needles, m.p. 97—98°. (Found: OCH_3 28.6; Br 25.0. Calc. for $C_{12}H_{15}O_5Br$ (319.2): OCH_3 29.2; Br 25.0.)

2. The same substance was obtained when a methanol solution of α,β-dibromo-hydroferulic acid (VII) was set aside overnight at room temperature and dry hydrogen chloride was subsequently passed into the solution for one hour (*cf.* Scheme 2). The substance decomposes on storage.

α,β-Dibromo-acetylhydroferulic acid (XX). α,β-Dibromo-hydroferulic acid (VII) (50 g) was dissolved by gentle warming in a mixture of 300 ml of acetic acid and 300 ml of acetic anhydride. After cooling 3 ml of conc. sulphuric acid was added dropwise. After two days standing at room temperature the mixture was poured onto ice. The resulting solid was recrystallized from benzene, forming prismatic plates, m.p. 166—167°. (Found: C 36.9; H 3.18; OCH_3 7.88. Calc. for $C_{12}H_{12}O_5Br_2$ (396.1): C 36.4; H 3.06; OCH_3 7.84.)

β-Bromo-3-methoxy-4-acetoxy-styrene (XXI). A solution of 17 g of α,β-dibromo-acetylhydroferulic acid (XX) in 400 ml of ethanol was refluxed with 12 g of potassium acetate for 8 hours. Potassium bromide was filtered off, the solution was evaporated and the residual oil was dissolved in chloroform. The chloroform solution was extracted with sodium bicarbonate solution, washed with water, dried over anhydrous sodium sulphate, and evaporated. After several days the oily residue had partly crystallized. Recrystallization from methanol yielded prismatic plates, m.p. 109—110°. (Found: C 48.7; H 4.07; OCH_3 11.8. Calc. for $C_{11}H_{11}O_3Br$ (271.1): C 48.7; H 4.09; OCH_3 11.5.)

SUMMARY

α,β-Dibromo-hydroferulic acid methyl ester has been prepared and converted into the corresponding β-hydroxy and β-acetoxy derivatives. Attempts

to replace the α-bromine atom in these derivatives by acetoxyl were unsuccessful. On acetylation both derivatives yielded α-bromo-β-acetoxy-acetylhydroferulic acid, in which the bromine is easily replaced by acetoxyl.

Similar attempts to obtain hydroxy and acetoxy derivatives of hydroferulic acid and its acetate are described.

Whereas ferulic acid and methyl ferulate are readily brominated in the side-chain, the corresponding acetyl compounds proved to be inert towards bromine.

REFERENCES

1. Adler, E., and Björkqvist, K. J. *Acta Chem. Scand.* **5** (1951) 241.
2. Adler, E., and Yllner, S. *Svensk Papperstidn.* **55** (1952) 238.
3. Adler, E., and Yllner, S. *Acta Chem. Scand.* **7** (1953) 570.
4. Zincke, Th., and Hahn, O. *Ann.* **329** (1903) 1.
5. Hoering, P. *Ber.* **40** (1907) 2174.
6. van Duin, C. F. *Rec. trav. chim.* **45** (1926) 348.
7. Vorsatz, F. *J. prakt. Chem.* [2] **145** (1936) 265; Pearl, I. A., and Beyer, D. L. *J. org. Chem.* **16** (1951) 216.
8. Posner, Th. *J. prakt. Chem.* [2] **82** (1910) 434.
9. Pacsu, E., and Stieber, Ch. *Ber.* **62** (1929) 2978.

Received September 17, 1952.