30. *The Chloroacetylation of Guaiacol.*

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Interaction of guaiacol, chloroacetic acid and phosphorus oxychloride at elevated temperatures yields principally 5-*αβ-dichlorovinylguaiacol chloroacetate* and very little of the expected 5-*chloroacetylguaiacol chloroacetate*; even at 100° appreciable amounts of the former are obtained. The orientation of the chief product has been ascertained by (i) hydrolysis and methylation, followed by the uptake of 3 mols. of hydrogen with formation of 2 mols. of hydrogen chloride and 4-ethylveratrole, (ii) ethylation and oxidation to *O*-ethyl*iso*vanillic acid. The 5-chloroacetylguaiacol chloroacetate was orientated by its hydrolysis and reduction to 5-ethylguaiacol, identified as its benzoate.

4-Chloroacetylguaiacol has previously been obtained in good yield by the interaction of veratrole and chloroacetyl chloride in the presence of aluminium chloride (Pratt and Robinson, *J.*, 1923, 753; cf. Tutin, *ibid.*, 1910, 2510) but there is no record of the direct production of the compound from guaiacol itself.

The acetylation of guaiacol yields products which depend largely upon the reaction conditions. Thus, 4-acetylguaiacol (acetovanillone) is obtained in 25% and 50% yields by the Fries rearrangement of guaiacol acetate in the presence of zinc chloride and aluminium chloride respectively, and the direct interaction of guaiacol and acetic acid in phosphoryl chloride solution at 100° gives 5-acetylguaiacol (*iso*acetovanillone) in a 20% yield (Coulthard, Marshall, and Pyman, *J.*, 1930, 280). Earlier, Reichstein (*Helv. Chim. Acta*, 1927, **10**, 392) had isolated 4-, 5-, and 6-acetylguaiacol from the rearrangement of guaiacol acetate with zinc chloride (cf. also Schneider and Kraft, *Ber.*, 1922, **55**, 1892).

During the course of synthesising Mannich bases containing a halogenated guaiacol residue it was observed that the interaction of guaiacol, chloroacetic acid and phosphorus oxychloride at elevated temperatures yields principally 5-αβ-*dichlorovinylguaiacol chloroacetate* together with guaiacol chloroacetate and only a very limited amount of the expected 5-*chloroacetylguaiacol chloroacetate*. These were separable by distillation. Even at 100° the dichlorovinyl derivative was formed in appreciable yield, although Krannichfeldt (*Ber.*, 1913, **46**, 4016) stated that guaiacol chloroacetate alone is formed under these conditions. Hydrolysis of the former with cold alkali gave 5-αβ-*dichlorovinylguaiacol* the constitution of which was proved by methylation to 4-αβ-*dichlorovinylveratrole* which on reduction with hydrogen and palladium-charcoal took up 3 mols. of hydrogen with formation of 4-ethylveratrole and liberation of 2 mols. of hydrogen chloride. Methylation of the αβ-dichlorovinylguaiacol followed by oxidation gave veratric acid whereas ethylation and oxidation yielded *O*-ethyl*iso*vanillic acid and this established the 5-position of the dichlorovinyl residue in the original dichlorovinylguaiacol. The orientation of the lesser product, 5-chloroacetylguaiacol chloroacetate, followed from its hydrolysis and reduction to 5-ethylguaiacol, identified as its benzoate.

It would appear that, by the reaction of the chloroacetic acid and phosphorus oxychloride on guaiacol, 5-chloroacetylguaiacol chloroacetate is initially formed and this, at the high temperature employed, is converted into 5-αβ-dichlorovinylguaiacol chloroacetate. This interpretation is supported by the yield of the 5-chloroacetylguaiacol chloroacetate being diminished and that of 5-αβ-dichlorovinylguaiacol chloroacetate being increased when the temperature is raised and the reaction time lengthened. The transformation may take place either by replacement of the hydroxyl group by chlorine in the *enol* form of the chloroacetylguaiacol chloroacetate, R·C(OH):CHCl, or by formation of 5-ααβ-trichloroethylguaiacol chloroacetate by direct chlorination of the *keto* form of the chloroacetylguaiacol chloroacetate, R·CO·CH_2Cl, with subsequent cleavage of hydrogen chloride. The latter hypothesis would accord, except for the nature of the chlorinating agent, with the formation from acetophenone and phosphorus pentachloride of αα-dichloroethylbenzene which on distillation loses hydrogen chloride to yield α-chlorostyrene (Dyckerhoff, *Ber.*, 1877, **10**, 119); also compare the similar formation of αβ-dichlorostyrene from ω-chloroacetophenone (Friedel, *Ann. Chim. Phys.*, 1869, **16**, 360; Béhal, *Bull. Soc. chim.*, 1888, **50**, 632; Kunckell and Eras, *Ber.*, 1900, **33**, 3264).

An improved synthesis of *O*-ethyl*iso*vanillic acid is described.

EXPERIMENTAL.

Interaction of Guaiacol, Chloroacetic Acid, and Phosphorus Oxychloride.—(*a*) *At* 170°. Guaiacol (75 g.), chloroacetic acid (200 g., 3·5 mols.) and phosphorus oxychloride (260 c.c., 5·5 mols.) were heated together in an oil-bath for 6 hours; the bath temperature, as the vigour of the reaction permitted, was raised from 110° to 170° over the first 3½ hours and then maintained at this temperature for 2½ hours. The product was cooled, poured on to an excess of powdered ice and the resulting liquor extracted three times with chloroform (900 c.c. in all). The chloroform extract was washed with dilute aqueous sodium bicarbonate and water, dried over calcium sulphate, the chloroform removed and the residual oil distilled. The fraction, b. p. 155—195°/0·3 mm. (92 g., 51%), consisting of 5-αβ-dichlorovinylguaiacol chloroacetate containing *ca.* 1% of 5-chloroacetylguaiacol chloroacetate, was collected. (In some experiments this was redistilled and the end fractions (3 g.) collected separately; the latter, on recrystallisation from benzene gave 5-chloroacetylguaiacol chloroacetate (*ca.* 0·5 g.), m. p. 130—134°). The crude product solidified on scratching and standing; it was recrystallised from ligroin (b. p. 40—60°)–diethyl ether (20 : 9 v/v) giving pure *5-αβ-dichlorovinylguaiacol chloroacetate* in silvery plates, m. p. 54—55° and b. p. 176—184°/0·5—0·6 mm., which very slowly turned pink (Found : C, 44·85; H, 3·3; Cl, 35·6. $C_{11}H_9O_3Cl_3$ requires C, 44·75; H, 3·1; Cl, 36·0%). The crude material was used for further work.

(*b*) *At* 150—155° Guaiacol (75 g.), chloroacetic acid (143 g., 2·5 mols.) and phosphorus oxychloride (92 c.c., 2 mols.) were heated under reflux in an oil bath (150—155° bath-temp.) for 3 hours. The reaction mixture was treated as above and gave the following fractions : (i), b. p. 120—130°/1 mm. (74 g.), consisting of guaiacol chloroacetate; (ii), b. p. 125°/0·8 mm. to 185°/0·6 mm. (5·9 g.), a viscous liquid; (iii), b. p. 185—200°/0·6 mm. (13·3 g.), and (iv), b. p. 200—230°/0·6 mm. (11·3 g.), a viscous liquid depositing a white solid.

Fractions (iii) and (iv) were separately diluted with equal volumes of carbon tetrachloride; on remaining at 0°, these deposited colourless crystals of 5-*chloroacetylguaiacol chloroacetate* (3·8 g.), m. p. 124—130°, and (6·3 g.), m. p. 132—134°, respectively. Recrystallisation of the combined crops from benzene gave 5-chloroacetylguaiacol chloroacetate in stout colourless needles, m. p. 133—134° (Found : C, 47·7; H, 3·8; Cl, 25·7; *M* (Rast), 281. $C_{11}H_{10}O_4Cl_2$ requires C, 47·7; H, 3·7; Cl, 25·6%; *M*, 277). Crude 5-αβ-dichlorovinylguaiacol chloroacetate was recovered from the first mother liquor.

4-*Chloroacetylguaiacol chloroacetate*, obtained from 4-chloroacetylguaiacol (Pratt and Robinson, *loc. cit.*) and chloroacetyl chloride in benzene solution, crystallised from ligroin–benzene in cream needles (Found : Cl, 26·2. $C_{11}H_{10}O_4Cl_2$ requires Cl, 25·6%). It had m. p. 93—95° which was depressed on admixture with the above 5-isomer.

(*c*) *At* 100°. Guaiacol (75 g.), chloroacetic acid (150 g., 2·6 mols.) and phosphorus oxychloride (200 c.c., 4·3 mols.) were heated on the water-bath for 4½ hours and the following fractions isolated as described above: (i), b. p. 125—130°/0·8 mm. (62 g.), consisted of guaiacol chloroacetate; it slowly solidified and, after crystallisation from ligroin, had m. p. 60°; (ii), b. p. 130—180°/0·7 mm. (5 g.), a viscous oil which deposited crystals of guaiacol chloroacetate on keeping; (iii), b. p. 180—220°/1·0 mm. (12·5 g.), a thick oil which slowly solidified, consisting chiefly of 5-αβ-dichlorovinylguaiacol chloroacetate.

5-*αβ-Dichlorovinylguaiacol.*—5-αβ-Dichlorovinylguaiacol chloroacetate (61 g.), dissolved in dioxan (400 c.c.), was added to 5N-sodium hydroxide (60 c.c., 1·5 equivalents) and the mixture gently warmed until a homogeneous solution was obtained. After the mixture had remained at 0° an equal volume of water was added, the solution acidified with 5N-sulphuric acid and extracted several times with ether (total, 1000 c.c.). The extract was dried over calcium sulphate, the ether removed and the residual oil distilled through a 14-cm. Vigreux column, the fraction, b. p. 140—142°/0·7 mm. (35·5 g.), being collected; this solidified on remaining at 0° and decomposed rapidly if not recrystallised at once. The solid (28·5 g.) on crystallisation from a mixture of ligroin (b. p. 40—60°) (100 c.c.), diethyl ether (15 c.c.) and benzene (5 c.c.) gave 5-*αβ-dichlorovinylguaiacol* (22 g.) in colourless prisms, m. p. 55—56°, stable after drying over sodium hydroxide under reduced pressure but becoming pink on long storage. For analysis a sample was dried over phosphoric oxide at 45—50°/1 mm. (Found : C, 49·2; H, 3·6; Cl, 32·5. $C_9H_8O_2Cl_2$ requires C, 49·3; H, 3·7; Cl, 32·4%).

The following acyl derivatives were obtained by standard methods : 5-*αβ-Dichlorovinylguaiacol acetate*, silvery plates from ligroin (b. p. 40—60°), m. p. 65·5—66·5° (Found : Cl, 27·0, 27·1. $C_{11}H_{10}O_3Cl_2$ requires Cl, 27·15%). 5-*αβ-Dichlorovinylguaiacol* p-*toluenesulphonate*, stout colourless needles from ligroin (b. p. 60—80°), m. p. 94—96° (Found : C, 51·3; H, 3·8; Cl, 19·0. $C_{16}H_{14}O_4Cl_2S$ requires C, 51·5; H, 3·8; Cl, 19·0%). 5-*αβ-Dichlorovinylguaiacol* p-*bromobenzenesulphonate*, fine colourless needles from ligroin (b. p. 60—80°), m. p. 95° (Found : 41·6; H, 2·5; Ag halide : substance, 1·096. $C_{15}H_{11}O_4Cl_2BrS$ requires C, 41·1; H, 2·6%; Ag halide : substance, 1·083). 5-*αβ-Dichlorovinylguaiacol* m-*nitrobenzenesulphonate*, colourless plates from benzene–methanol, m. p. 84—85° (Found : C, 44·5; H, 2·85; Cl, 17·5. $C_{15}H_{11}O_6NCl_2S$ requires C, 44·5; H, 2·75; Cl, 17·55%).

5-*Chloroacetylguaiacol.*—When the crude and once distilled ester (62 g.), b. p. 155—195°/0·3 mm., was hydrolysed as above the crude phenol obtained on crystallisation from ligroin–ether–benzene yielded a small amount of white solid which had a very low solubility in the mixture. This was separately crystallised from benzene and gave long colourless needles (0·3 g.) of 5-*chloroacetylguaiacol* (Found : C, 54·2; H, 4·6; Cl, 18·3. $C_9H_9O_3Cl$ requires C, 54·0; H, 4·5; Cl, 17·7%). It had m. p. 121—122°, depressed to 75—85° on admixture with 4-chloroacetylguaiacol (m. p. 102—104°, Pratt and Robinson, *loc. cit.*).

4-*αβ-Dichlorovinylveratrole.*—A solution of 5-αβ-dichlorovinylguaiacol (25 g.) in dry methanol (40 c.c.) was added to a solution of sodium (2·65 g.) in methanol (100 c.c.) followed by addition of methyl iodide (15 c.c.) and the resulting solution refluxed for 5 hours. The solvent was distilled away under reduced pressure, the residual oil mixed with water (50 c.c.) and extracted several times with ether (200 c.c. in all); the ethereal extract was treated with a small amount of sulphur dioxide to remove iodine, dried over potassium carbonate, the ether removed and the residual oil distilled. The fraction (22·9 g.), b. p. 147—149°/1 mm., was 4-*αβ-dichlorovinylveratrole*; this was a pale yellow viscous oil which did not crystallise and decomposed slowly on keeping (Found : Cl, 30·6. $C_{10}H_{10}O_2Cl_2$ requires Cl, 30·5%). When dissolved in cold carbon tetrachloride, it did not take up bromine.

Oxidation of 4-*αβ-Dichlorovinylveratrole to Veratric Acid.*—The foregoing compound (9·5 g.) was rapidly stirred with water (150 c.c.) at 70—80° and a solution of potassium permanganate (29 g.) in water (350 c.c.) run in over 45 minutes.

The mixture was stirred for another hour at this temperature, basified with potassium hydroxide, filtered and the residue well washed into the filtrate. The latter was concentrated to *ca.* 200 c.c., acidified and kept at 0°; the precipitate was collected (2·5 g.) and crystallised from benzene, veratric acid being obtained in colourless needles, m. p. 180—182° alone and in admixture with an authentic specimen (Found: C, 59·7; H, 5·5; *M*, by titration, 181·5. Calc.: C, 59·4; H, 5·5%; *M*, 182).

Hydrogenation of 4-αβ-*Dichlorovinylveratrole to* 4-*Ethylveratrole*.—A solution of 4-αβ-dichlorovinylveratrole (5·0 g.) in ethanol (200 c.c.) and water (50 c.c.) was shaken in an atmosphere of hydrogen at 25°/800 mm. in the presence of a palladium catalyst prepared from palladium chloride (0·1 g.) and charcoal (10 g.). Absorption (1605 c.c. of hydrogen at 25°/744 mm.; calc.: (3 mols.) 1610 c.c.) was complete in 80 minutes. The catalyst was separated and washed with boiling water into the filtrate which required 56·7 c.c. of 0·778N-potassium hydroxide for neutralisation to phenolphthalein, corresponding to 0·0441 equivalents of hydrogen chloride (calc.: 0·0439 equivalents). The solutions from two hydrogenations were combined, the alcohol was removed, the residue extracted with ether, the extract dried and distilled. 4-Ethylveratrole (7·3 g.), b. p. 115—120°/14 mm., was obtained (Barger and Silberschmidt, *J.*, 1928, 2919, give b. p. 110—112°/9 mm.). On redistillation, 4·7 g. had b. p. 118—120°/14 mm. (Found: C, 72·35; H, 8·6. Calc.: C, 72·35; H, 8·5%).

The foregoing compound (3·5 g.) was stirred with water (80 c.c.) at 95° and potassium permanganate (24 g.) dissolved in boiling water (300 c.c.) added over 3 hours. The filtered solution was concentrated to *ca.* 100 c.c., acidified and strongly cooled. The colourless precipitate was crystallised from benzene (charcoal), yielding veratric acid (0·1 g.) in colourless needles, m. p. and mixed m. p. 180—182° (Found: *M*, 185).

5-αβ-*Dichlorovinylguaiacol Ethyl Ether*.—5-αβ-Dichlorovinylguaiacol (14·2 g.) dissolved in ethanol (40 c.c.) was added to a solution of sodium (1·4 g.) in alcohol (60 c.c.) followed by ethyl bromide (10 c.c.) and the mixture refluxed for 4 hours. After removal of the sodium bromide, the alcohol was removed, leaving an oil which slowly solidified. Crystallisation from ligroin (b. p. 80—100°) gave 5-*αβ-dichlorovinylguaiacol ethyl ether* (9·6 g.) in colourless needles, m. p. 74—76° (Found: C, 53·6; H, 4·75; Cl, 28·4. $C_{11}H_{12}O_2Cl_2$ requires C, 53·5; H, 4·9; Cl, 28·7%).

O-*Ethyl*iso*vanillic Acid*.—The foregoing compound (8 g.) was stirred with water (200 c.c.) and a solution of potassium permanganate (15 g.) in water added during 1 hour; during the addition the temperature was maintained at 70—80° and the mixture then stirred for a further 1 hour. The crude acid, isolated in the usual manner, on crystallisation from benzene–toluene (4 : 1) gave *O*-ethyl*iso*vanillic acid (3 g.) in colourless needles, m. p. 164—166° alone and in admixture with the synthetic material from nitro-*p*-tolyl methyl ether described below (Found: C, 60·8; H, 5·9; *M*, by titration, 196·5. Calc.: C, 61·2; H, 6·2%; *M*, 196).

Clemmensen Reduction of 5-αβ-*Dichlorovinylguaiacol to* 5-*Ethylguaiacol*.—5-αβ-Dichlorovinylguaiacol (10 g.), amalgamated zinc (100 g.) and 3·3N-hydrochloric acid (300 c.c.) were refluxed for 10¼ hours, benzene (80 c.c.) added and the whole refluxed for a further 7 hours. The layers were separated, the aqueous layer together with the residue extracted with benzene and the combined benzene solutions dried over calcium sulphate and distilled. 5-Ethylguaiacol (5·25 g.) was obtained as a colourless oil, b. p. 78—82°/2 mm., which solidified on strong cooling. Crystallisation from ligroin (b. p. 30—40°) gave the pure compound in colourless plates, m. p. 37·5—38·5 (lit., 35—36°) (Found: C, 70·6; H, 8·0. Calc.: C, 71·0; H, 8·0%). The benzoate had b. p. 175—180°/2 mm. and crystallised from ligroin (b. p. 40—60°) in large colourless prisms, m. p. 53·5—55·5° (lit., 53°) (Found: C, 75·0; H, 6·2. Calc.: C, 75·0; H, 6·3%). The *acetate* crystallised from ligroin (b. p. 30—40°) in colourless plates, m. p. 34—35° (Found: C, 67·6; H, 7·2. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·3%).

Hydrolysis and Clemmensen Reduction of 5-*Chloroacetylguaiacol Chloroacetate*.—5-Chloroacetylguaiacol chloroacetate (3 g.) was reduced by the Clemmensen method and the crude 5-ethylguaiacol (0·8 g., b. p. 124—125°/20 mm.) benzoylated in aqueous alkaline solution, the latter extracted with chloroform, the chloroform extract dried and distilled, the fraction b. p. 178—180°/2 mm. being collected (0·6 g.). This on crystallisation from ligroin (b. p. 40—60°) gave 5-ethylguaiacol benzoate in colourless prisms (0·45 g.), m. p. 53·5—55·5° alone and in admixture with a sample obtained from the reduction of 5-αβ-dichlorovinylguaiacol.

2-*Nitro*-4-*methylanisole*.—This was obtained from 2-nitro-4-methylphenol (53·5 g.) as described by Schultz (*Ber.*, 1907, **40**, 4324) but the crude product was distilled in superheated steam (oil bath temp. 200°); the 2-nitro-4-methylanisole distilled as a yellow oil (37 g.) in *ca.* 1 l. of distillate (cf. Brasch and Freyss, *Ber.*, 1891, **24**, 1960, and De Vries, *Rec. trav. chim.*, 1909, **28**, 284). The nitro compound (51 g.) was stirred on the water-bath with water (130 c.c.) and 10N-hydrochloric acid (5 c.c.) and finely divided iron powder ("Pacteron No. 2," 55 g.) added gradually during 2¼ hours; more iron powder (20 g.) was then added and the stirring continued for another 2 hours. After the addition of saturated aqueous sodium carbonate (20 c.c.) the mixture was distilled in superheated steam (oil-bath temp. 200°). This distillate (2·5 l.) was saturated with sodium chloride, extracted with ether, the extract dried and distilled. 2-Amino-4-methylanisole (30 g.) distilled as an oil, b. p. 136—140°/29 mm., which solidified on cooling (cf. De Vries, *loc. cit.*, and Robinson, *J.*, 1916, 1088).

5-*Methylguaiacol*.—2-Amino-4-methylanisole (20 g.) dissolved in water (130 c.c.) and sulphuric acid (10·9 c.c.) was diazotised at 2° by the addition of a solution of sodium nitrite (11·5 g.) in water (37 c.c.). The diazo solution was added slowly to a solution of anhydrous sodium sulphate (115 g.) in water (87 c.c.) and sulphuric acid (87 c.c.) which, during the whole addition, was heated in an oil-bath (temp. 150° rising to 180°) and through which a current of dry steam was passing. The distillate (1·3 l.) was saturated with sodium chloride, repeatedly extracted with benzene (total, 250 c.c.), and the benzene solution dried and distilled. 5-Methylguaiacol (11·3 g.) distilled as a yellow oil, b. p. 83—86°/3 mm., which solidified to a mass of yellow plates (Limpach, *Ber.*, 1889, **22**, 350 and De Vries, *loc. cit.* give b. p. 222°/760 mm. and 180°/250 mm., respectively).

5-*Methylguaiacol Ethyl Ether*.—Ethyl sulphate (19 c.c.) was added in portions to a shaken solution of 5-methylguaiacol (13·4 g.) in water (30 c.c.) and 5N-sodium hydroxide (32 c.c.) heated on the water bath during 15 minutes. Heating was continued for a further 1½ hours, ammonia (20 c.c., *d* 0·880) added and the mixture distilled in steam. Ether extraction of the distillate followed by fractionation gave 5-*methylguaiacol ethyl ether* as a colourless oil (13 g.) which, on redistillation, had b. p. 120°/30 mm. (Found: C, 72·5; H, 8·6. $C_{10}H_{14}O_2$ requires C, 72·35; H, 8·5%).

O-*Ethyl*iso*vanillic Acid*.—The foregoing ether (4·2 g.) was rapidly stirred with water (100 c.c.) at 90—95° and a boiling solution of potassium permanganate (12 g.) in water (150 c.c.) added slowly over 1½ hours; after heating at 90° for a further 1½ hours the product was isolated in the usual way. The crude acid (2·25 g.) was recrystallised from ligroin (b. p. 80—100°)–benzene (10 : 1) giving *O*-ethyl*iso*vanillic acid (1·8 g.) in colourless needles, m. p. 164—166° (Found: C, 61·3; H, 6·1; *M*, by titration, 194·5. Calc.: C, 61·2; H, 6·2%; *M*, 196).

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