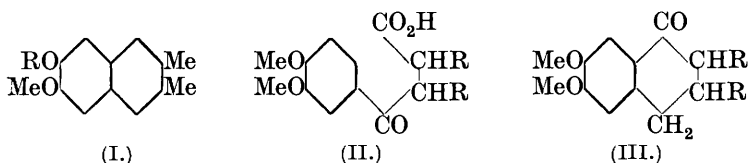


## 198. *The Constituents of Guaiacum Resin. Part I. Synthesis of Pyroguaiacin Methyl Ether.*

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OUR knowledge of the nature of guaiacum resin is due largely to the investigations of Herzig (*Monatsh.*, 1892, **13**, 822; 1897, **18**, 714; 1898, **19**, 95) and Doebner (*Arch. Pharm.*, 1896, **234**, 590, 610, 614). Three phenolic substances, guaiaretic, guaiaconic, and guaiacic acids, have been isolated by the action of alkali on the resin. Schroeter, Lichtenstadt, and Irineu (*Ber.*, 1918, **51**, 1537) have assigned a constitution to the crystalline guaiaretic acid, but the so-called guaiaconic and guaiacic acids are probably heterogeneous (see Richter, *Arch. Pharm.*, 1906, **244**, 90; Schroeter, Lichtenstadt, and Irineu, *loc. cit.*).

Most of the evidence relating to the structure of the resin and the constituent acids has been obtained from a study of their dry distillation products. When guaiacum resin is distilled it yields guaiacol, creosol, tiglic aldehyde, and pyroguaiacin along with unrecognisable products. Pyroguaiacin was first isolated by Wieser (*Wien. Akad. Ber.*, 1881, 464) and later work has shown that it is a methoxy-phenol,  $C_{13}H_{14}O_2$ . Wieser showed that it was converted into guaiacene,  $C_{12}H_{12}$ , by distillation with zinc dust and the synthetic experiments of Schroeter, Lichtenstadt, and Irineu (*loc. cit.*) proved guaiacene to be 2:3-dimethylnaphthalene. These authors suggested that pyroguaiacin is a hydroxymethoxyguaiacene of structure (I; R = H), and this structure has now been confirmed by the synthesis of its methyl ether (I; R = Me).



Preliminary experiments were carried out in order to devise a suitable method of converting veratrole into dimethoxynaphthalene derivatives.

$\beta$ -3:4-Dimethoxybenzoylpropionic acid (II; R = H) (Bargellini and Giua, *Gazzetta*, 1912, **42**, 197) was reduced to  $\gamma$ -3:4-dimethoxyphenylbutyric acid, which was converted into 1-keto-6:7-dimethoxy-1:2:3:4-tetrahydronaphthalene (III; R = H). The ketone (III) was reduced to the corresponding tetrahydronaphthalene, which when dehydrogenated with selenium yielded the 2:3-dimethoxynaphthalene of Friedländer and Silberstein (*Monatsh.*, 1902, **28**, 520)

and Kauffmann and Beisswenger (*Ber.*, 1903, **36**, 569). The ketone (III) was also condensed with methylmagnesium iodide, and the product dehydrogenated to 6 : 7-dimethoxy-1-methylnaphthalene, prepared by Luff, Perkin, and Robinson (*J.*, 1910, **97**, 1132).

The synthesis of pyroguaiacin methyl ether was effected by a similar series of reactions using  $\alpha\beta$ -dimethylsuccinic anhydride (Higson and Thorpe, *J.*, 1906, **89**, 1463), both the *cis*- and the *trans*-form of which, when condensed with veratrole, yielded the same  $\beta$ -3 : 4-dimethoxybenzoyl- $\alpha\beta$ -dimethylpropionic acid (II; R = Me), which was converted into 1-keto-6 : 7-dimethoxy-2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (III; R = Me), and pyroguaiacin methyl ether. The synthetical product and its derivatives agree in properties with the corresponding substances obtained by Schroeter, Lichtenstadt, and Irineu (*loc. cit.*) from guaiacum resin, but a direct comparison has not been made.

#### EXPERIMENTAL.

$\beta$ -3 : 4-Dimethoxybenzoylpropionic Acid (II; R = H).—After veratrole (16 g.) and succinic anhydride (11 g.) had been kept in a solution of anhydrous aluminium chloride (30 g.) in nitrobenzene (100 c.c.) for 24 hours, dilute hydrochloric acid was added, and the mixture distilled in steam. The residue was filtered hot, and  $\beta$ -3 : 4-dimethoxybenzoylpropionic acid (22.2 g.) separated from the cooled filtrate. It crystallised from boiling water in colourless prisms, m. p. 160—161° (Found: C, 60.3; H, 6.1. Calc. for  $C_{12}H_{14}O_5$ : C, 60.5; H, 5.9%).

$\gamma$ -3 : 4-Dimethoxyphenylbutyric Acid.—The preceding acid (10 g.), concentrated hydrochloric acid (22 c.c.), and amalgamated zinc (14 g.) were boiled for 4 hours. After dilution with water the product was isolated by means of ether, dissolved in sodium bicarbonate solution, shaken with ether, acidified, extracted and dried (sodium sulphate) in ether, recovered, and distilled at 0.2 mm. The distillate crystallised from chloroform-light petroleum (b. p. 60—80°) in colourless prisms, m. p. 57—59° (Found: equiv., 230.  $C_{12}H_{16}O_4$  requires equiv., 224). The acid on treatment with bromine in acetic acid gave  $\gamma$ -2-bromo-4 : 5-dimethoxyphenylbutyric acid, which crystallised from aqueous acetic acid in colourless prisms, m. p. 135—136° (Found: equiv., 298.  $C_{12}H_{15}O_4Br$  requires equiv., 303).

1-Keto-6 : 7-dimethoxy-1 : 2 : 3 : 4-tetrahydronaphthalene (III; R = H).— $\gamma$ -3 : 4-Dimethoxyphenylbutyric acid (4 g.) and 95% sulphuric acid (8 c.c.) were heated on the water-bath for  $\frac{1}{2}$  hour. An ethereal extract of the diluted solution was washed with water and then with dilute aqueous ammonia, dried with potassium carbonate, and freed

from solvent; the residue (3 g.) crystallised from petroleum (b. p. 100—120°) in colourless well-defined prisms, m. p. 98—99° (Found: C, 69.9; H, 6.7.  $C_{12}H_{14}O_3$  requires C, 69.9; H, 6.8%). The *oxime* crystallised from alcohol in long needles, m. p. 157—158° (Found: N, 6.5.  $C_{12}H_{15}O_3N$  requires N, 6.3%), and the semicarbazone from much alcohol in small crystals, m. p. 247—249° (decomp.).

*6 : 7-Dimethoxy-1-methylnaphthalene*.—The ketotetrahydronaphthalene derivative (III; R = H) (2 g.) in ether (30 c.c.) was treated with the methylmagnesium iodide prepared from magnesium (0.3 g.) and methyl iodide (1.1 c.c.) in ether (15 c.c.). The mixture was warmed for 1 hour and decomposed with ammonium chloride, and from the washed and dried ethereal solution a brown oil was isolated. This was heated with formic acid (5 c.c.) on the water-bath for 10 minutes. From the mixture, diluted with water, ether extracted a substance, which was heated with selenium (5 g.) for 24 hours at 300—330°. *6 : 7-Dimethoxy-1-methylnaphthalene*, extracted in light petroleum (b. p. 60—80°) and distilled over sodium at 0.2 mm., crystallised from alcohol in colourless plates, m. p. 110—111° (Found: C, 77.4; H, 7.1.  $C_{13}H_{14}O_2$  requires C, 77.2; H, 6.9%). The *picrate* crystallised from alcohol in long orange needles, m. p. 116—117° (Found: N, 10.0.  $C_{19}H_{17}O_9N_3$  requires N, 9.8%).

*2 : 3-Dimethoxynaphthalene*.—The ketotetrahydronaphthalene (III; R = H) (1.4 g.), amalgamated zinc (2.3 g.), and concentrated hydrochloric acid (3 c.c.) were boiled for 12 hours. The product was isolated in ether, distilled at 0.2 mm., and heated (1 g.) with selenium (2 g.) at 270—290° for 16 hours. *2 : 3-Dimethoxynaphthalene*, isolated in chloroform, crystallised from light petroleum (b. p. 60—80°) in colourless jagged prisms, m. p. 115—117° (Found: C, 76.4; H, 6.5. Calc. for  $C_{12}H_{12}O_2$ : C, 76.6; H, 6.4%). The *picrate* crystallised from methyl alcohol in slender orange needles, m. p. 131—132° (Found: N, 10.2.  $C_{18}H_{15}O_9N_3$  requires N, 10.1%).

*β-3 : 4-Dimethoxybenzoyl-αβ-dimethylpropionic Acid* (II; R = Me).—Veratrole (4 g.) and *cis*- or *trans*-αβ-dimethylsuccinic anhydride (3.6 g., distilled under reduced pressure), were added to a solution of anhydrous aluminium chloride (8.4 g.) in nitrobenzene (20 c.c.). After 24 hours, dilute hydrochloric acid was added, the mixture distilled in steam, the residual oil extracted with ether, and the *acid* dissolved in sodium bicarbonate solution, recovered, and crystallised from dilute acetic acid, forming white plates (2.9 g.), m. p. 165—166° (Found: C, 63.3; H, 6.9; equiv., 269.  $C_{14}H_{18}O_5$  requires C, 63.2; H, 6.8%; equiv., 266).

*1-Keto-6 : 7-dimethoxy-2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene* (III; R = Me).—The acid (II; R = Me) (2 g.), concentrated hydrochloric acid (4 c.c.), and amalgamated zinc (2.6 g.) were boiled

for 4 hours. The product, isolated by ether extraction and purified by solution in sodium bicarbonate, was an oil, which was converted into (III; R = Me) by warming with 90% sulphuric acid (4 c.c.) on the water-bath for  $\frac{1}{2}$  hour. The deep red solution was diluted with water and extracted with chloroform, the extract washed with water and aqueous ammonia and dried, the solvent removed, and the residue distilled at 0.2 mm. The distillate crystallised from light petroleum (b. p. 60—80°) in jagged prisms (0.5 g.), m. p. 135—136° (Found : C, 71.8; H, 7.8.  $C_{14}H_{18}O_3$  requires C, 71.8; H, 7.7%).

*Pyroguaiacin Methyl Ether* (I; R = Me).—The ketotetrahydro-naphthalene (III; R = Me) (0.6 g.) was reduced with zinc (0.9 g.) and concentrated hydrochloric acid (1.5 c.c.) for 12 hours. The product, isolated with ether, was a brown oil (0.56 g.), which was heated with selenium (5 g.) at 280—320° for 20 hours. The crude naphthalene derivative was extracted in light petroleum and crystallised from methyl alcohol and then from light petroleum (b. p. 60—80°); colourless needles, m. p. 149—150° (S. L. and I. give 149—150°) were obtained (Found : C, 77.5; H, 7.4. Calc. for  $C_{14}H_{16}O_2$  : C, 77.8; H, 7.4%). The *picrate* separated from methyl alcohol in long red needles, m. p. 130—131° (Found : N, 9.6.  $C_{20}H_{19}O_9N_3$  requires N, 9.4%). The quinone, prepared as described by Schroeter, Lichtenstadt, and Irineu, who give m. p. 241—242° (*loc. cit.*), crystallised from glacial acetic acid in slender yellow needles, m. p. 241—242°.

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