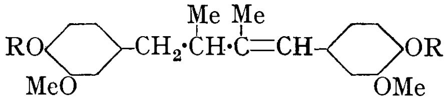
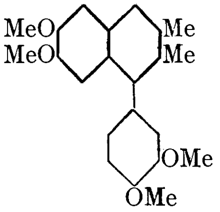
311. *The Constituents of Guaiacum Resin. Part II. Synthesis of* dl-*Guaiaretic Acid Dimethyl Ether.*

By Robert D. Haworth, Cecil R. Mavin, and George Sheldrick.

Guaiaretic acid, which occurs to an extent of 12% in guaiacum resin, was given the formula $C_{20}H_{26}O_4$ by Herzig and Schiff (*Monatsh.*, 1897, **18**, 714; 1898, **19**, 95), who demonstrated the presence of two phenolic hydroxyl groups, and recognised guaiacol and pyroguaiacin as products of distillation. Doebner and Lücker (*Arch. Pharm.*, 1896, **234**, 590) suggested $C_{20}H_{24}O_4$ as the molecular formula, and this was confirmed by the work of Schroeter, Lichtenstadt, and Irineu (*Ber.*, 1918, **51**, 1537), who suggested the structural formula (I; R = H)[*] for guaiaretic acid. This formula accounts for the optical activity of the phenol and for the fact that reduction of the double bond gave an optically inactive dihydro-derivative. The conversion of guaiaretic acid dimethyl ether into naphthalene derivatives, such as dehydroguaiaretic acid dimethyl ether (II; see Schroeter, Lichtenstadt, and Irineu) and pyroguaiacin (see synthesis, Part I, J., 1932, 1485), is readily explicable on the basis of this formula.

(I.)



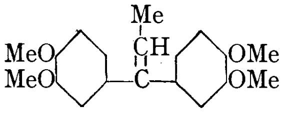


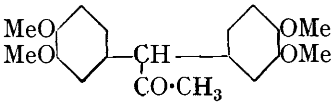
(II.)

The present communication describes a number of experiments designed to synthesise compounds of the dehydroguaiaretic or guaiaretic acid type, and which succeeded in the case of dl-*guaiaretic acid dimethyl ether* (I; R = Me).

Attempts to synthesise dehydroguaiaretic acid dimethyl ether by condensing 1-keto-6 : 7-dimethoxy-2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (J., 1932, 1487) with 4-iodoveratrole were unsuccessful, because of the difficulty experienced in the preparation of the Grignard reagent of the latter. Some experiments were made with 3 : 4 : 3′ : 4′-tetramethoxybenzophenone (Perkin, Smith, and Weizmann, J., 1906, **89**, 1661), which reacted with ethylmagnesium iodide to give αα-*bis*-3 : 4-*dimethoxyphenyl*-Δ^{α}-*propylene* (III). Treatment of this with perbenzoic acid gave as.-*bis*-3 : 4-*dimethoxyphenylacetone* (IV), but the small yields obtained, and the fact that the ketone did not react smoothly with ethyl α-bromopropionate, caused us to abandon this scheme.

(III.)



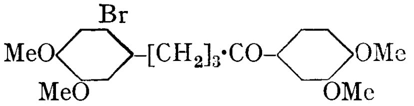


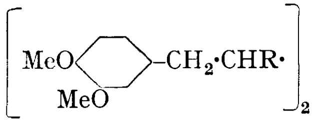
(IV.)

Preliminary experiments indicated that acids such as γ-3 : 4-dimethoxyphenylbutyric acid (J., 1932, 1486) might be used in the synthesis of guaiaretic acid derivatives. The chloride of this acid did not condense with veratrole in the presence of aluminium chloride on account of the ease with which it was converted into 1-keto-6 : 7-dimethoxy-1 : 2 : 3 : 4-tetrahydronaphthalene, but α-*veratroyl*-γ-(2-*bromo*-4 : 5-*dimethoxyphenyl*)*propane* (V) was obtained by the action of γ-2-bromo-4 : 5-dimethoxyphenylbutyryl chloride on veratrole. This ketone (V) was reduced by Clemmensen's method to 2-*bromo*-αδ-*bis*-4 : 5-*dimethoxyphenylbutane*, which was reduced catalytically to αδ-*bis*-3 : 4-*dimethoxyphenylbutane*

[*] The formula given by those authors (*loc. cit.*, p. 1593) differs from (I; R = H); the positions of the hydroxyl and methoxyl groups are interchanged in one of the aromatic rings. This is doubtless a typographical error, for Schroeter (*Chem. Zentr.*, 1928, II, 2303) refers to guaiaretic acid as a dimeride of *iso*eugenol. The formula (I; R = H) is employed by Meyer–Jacobson (Vol. II, Part IV, p. 162)

(VI; R = H). It was therefore expected that dihydroguaiaretic acid dimethyl ether (VI; R = Me) would be obtained by a similar series of reactions from γ-(*2-bromo-*4 : 5-

(V.)




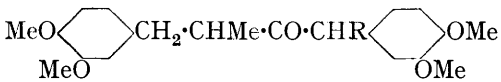
(VI.)

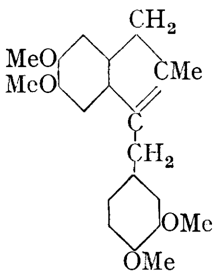
dimethoxyphenyl)-*αβ-dimethylbutyric acid.* However, the only crystalline product which could be isolated from the reaction between the chloride of this acid and veratrole was 1-keto-6 : 7-dimethoxy-2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene. This curious result, involving debromination, could not be avoided by varying the conditions of the experiment.

Beckh (*Ber.*, 1898, **31**, 3150) showed that phenylacetonitrile reacted with esters to yield β-keto-nitriles, and with a view to utilising this reaction, *α-cyano-αδ-diphenylbutan-β-one* (VII; R = CN) was prepared by the condensation of phenylacetonitrile and methyl β-phenylpropionate in the presence of potassium ethoxide. This cyano-ketone was hydrolysed by means of cold fuming hydrochloric acid to the corresponding *amide* (VII; R = CO·NH₂), which was converted into αδ-diphenylbutan-β-one (VII; R = H) by boiling concentrated hydrochloric acid. This ketone reacted with methylmagnesium iodide to give a carbinol, which was dehydrated by means of formic acid to αδ-diphenyl-β-methyl-Δ$^{\alpha}$-butene (VIII), isolated as its *dibromo*-compound.

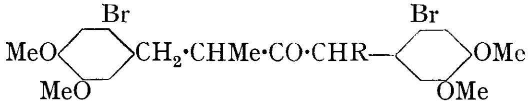
(VII.) $CH_2Ph{\cdot}CH_2{\cdot}CO{\cdot}CHRPh$ $\qquad$ $CH_2Ph{\cdot}CH_2{\cdot}CMe{:}CHPh$ (VIII.)

Similar reactions were then carried out with 3 : 4-dimethoxyphenylacetonitrile and *methyl* β-3 : *4-dimethoxyphenyl-α-methylpropionate,* which condensed to give the oily cyano-ketone (IX; R = CN); this was hydrolysed by means of cold fuming hydrochloric acid to β-*keto-αδ-bis-*3 : *4-dimethoxyphenyl-γ-methylvaleramide* (IX; R = CO·NH₂). Abnormal results were obtained when this amide was boiled with concentrated hydrochloric acid. Instead of the desired ketone (IX; R = H), a crystalline non-ketonic compound, probably 3′ : 4′ : 5 : 6-*tetramethoxy-*3*-benzyl-*2*-methylindene* (X), was obtained. This compound reacted with methylmagnesium iodide with evolution of methane, and contained a double bond, which could be reduced catalytically to a crystalline *dihydro*-derivative. In an endeavour to prevent this indene formation, 2*-bromo-*4 : 5*-dimethoxyphenylacetonitrile* and methyl β-(2*-bromo-*4 : 5*-dimethoxyphenyl*)*-α-methylpropionate* were condensed to yield *α-cyano-αδ-bis-*2*-bromo-*4 : 5*-dimethoxyphenyl-γ-methylbutan-β-one* (XI; R = CN), which was readily converted into β*-keto-αδ-bis-*2*-bromo-*4 : 5*-dimethoxyphenyl-γ-methylvaleramide* (XI; R = CO·NH₂). This amide was hydrolysed by means of boiling hydrochloric acid to *αδ-bis-*2*-bromo-*4 : 5*-dimethoxyphenyl-γ-methylbutan-β-one* (XI; R = H), but attempts to condense this with Grignard reagents were unsuccessful; the material was recovered unchanged under normal conditions, and reaction at elevated temperatures resulted in demethylation of the methoxyl groups. Eventually, it was found that the amide

(IX.)




(X.)

(XI.)


(IX; R = CO·NH₂) was converted by boiling with dilute hydrochloric acid into an oil containing *αδ-bis-*3 : *4-dimethoxyphenyl-γ-methylbutan-β-one* (IX; R = H), which was detected by means of its crystalline *dinitro*-derivative, but could not be purified sufficiently for subsequent stages of the synthesis. Better results were obtained by subjecting the amide (IX; R = CO·NH$_2$) to alkaline hydrolysis; the ketone (IX; R = H) was obtained in 30% yields as an oil, which was converted quantitatively into the crystalline dinitro-derivative and reacted smoothly with methylmagnesium iodide. The resultant carbinol was dehydrated with potassium hydrogen sulphate to give *dl*-guaiaretic acid dimethyl ether (I; R = Me), m. p. 112—113°. This was reduced with hydrogen in the presence of palladised charcoal to *dl*-dihydroguaiaretic acid dimethyl ether (VI; R = Me), m. p. 101—102°, identical with an optically inactive specimen kindly supplied by Professor Schrœter. Further, the dinitro- and the dibromo-derivative and αδ-bis-3 : 4-dihydroxyphenyl-βγ-dimethylbutane obtained from the synthetic specimen were identical with the corresponding compounds prepared from the natural product.

Schroeter, Lichtenstadt, and Irineu (*loc. cit.*) discovered that optically active guaiaretic acid dimethyl ether was converted into a mixture of the dimethyl ethers of dehydroguaiaretic (II) and dihydroguaiaretic acids (VI; R = Me) by the action of Hübl's iodine solution. It has now been observed that, under similar conditions, synthetic *dl*-guaiaretic acid dimethyl ether is oxidised to (II) in excellent yields, but no reduction product (VI; R = Me) could be detected. Professor Schroeter informs us (private communication) that recent work carried out in his laboratory has shown that both the optically active and the inactive form of dihydroguaiaretic acid (VI; R = H) occur naturally in guaiacum resin, and that crude guaiaretic acid (I; R = H), contaminated with these products, was used in some of his earlier experiments. The discrepancy between the synthetic and the natural product, mentioned above, can be explained by the incomplete removal of the dihydro-derivative from the guaiaretic acid employed in the degradation experiments.

EXPERIMENTAL.

αα-*Bis*-3 : 4-*dimethoxyphenyl*-Δ$^{\alpha}$-*propylene* (III).—A solution of ethylmagnesium iodide (from ethyl iodide, 6 c.c., and magnesium, 1·7 g., in ether, 30 c.c.) was gradually added with stirring to a solution of 3 : 4 : 3′ : 4′-tetramethoxybenzophenone (8·8 g.) in benzene (50 c.c.), and the mixture boiled for 2½ hours. Dilute sulphuric acid was added, the benzene layer removed and dried, and the solvent evaporated. The residual carbinol was dehydrated by heating at 100° with 98% formic acid (10 c.c.) for ½ hour, and the product, isolated with ether, was distilled under reduced pressure. The *propylene* (III) (6·6 g.), b. p. 200—205°/0·3 mm., rapidly solidified, and crystallised from methyl alcohol in colourless prisms (4·3 g.), m. p. 78—79° [Found: C, 72·3; H, 7·1; *M* (Rast), 322. $C_{19}H_{22}O_4$ requires C, 72·6; H, 7·0%; *M*, 314]. It rapidly decolorised bromine in chloroform solution and potassium permanganate in acetone solution. A second fraction, b. p. 220—270°/0·3 mm., was obtained which yielded colourless slender needles, m. p. 154—155°, after three crystallisations from methyl alcohol [Found: C, 70·4; H, 6·9; *M* (Rast), 420. $C_{25}H_{28}O_6$ requires C, 70·7; H, 6·6%; *M*, 424]. This substance, which is saturated, may be *triveratrylmethane*, produced as a result of profound change during the high-temperature distillation.

as.-*Bis*-3 : 4-*dimethoxyphenylacetone* (IV).—The above propylene derivative (III) (2·9 g.) was added to a solution of perbenzoic acid (2·7 g.) in chloroform (100 c.c.). After 3 days, the solution was washed, first with 4% sodium hydroxide solution and then with 10% sulphuric acid, dried, the solvent removed, and the dark brown residue distilled. The distillate, b. p. 210—250°/0·3 mm., was crystallised first from methyl alcohol and then from light petroleum (b. p. 80—100°); stout prisms (0·2 g.), m. p. 123—124°, were obtained (Found: C, 69·1; H, 6·5. $C_{19}H_{22}O_5$ requires C, 69·1; H, 6·6%).

α-*Veratroyl*-γ-(2-*bromo*-4 : 5-*dimethoxyphenyl*)*propane* (V).—γ-2-Bromo-4 : 5-dimethoxyphenylbutyric acid (J., 1932, 1486) (5·3 g.) was gently warmed for 2 hours with thionyl chloride (6 c.c.), and excess of the latter removed. The crystalline residue was dissolved in nitrobenzene (10 c.c.) and added with shaking to an ice-cold mixture of nitrobenzene (30 c.c.), veratrole (13 c.c.), and aluminium chloride (5·9 g.). After 24 hours, dilute hydrochloric acid was added, the nitrobenzene and excess of veratrole were removed in steam, and the residue was extracted with ether, washed with sodium hydroxide solution, and dried. The residual brown oil (6·4 g.) gave a *semicarbazone* (6 g.), pale yellow needles, m. p. 172—173° (Found: Br, 16·4. $C_{21}H_{26}O_5N_3Br$ requires Br, 16·6%), from alcohol. This (1·5 g.) was stirred for 2 hours at 110° with an aqueous solution of oxalic acid, saturated at 100° (30 c.c.), and poured into water;

the *ketone* (V) was isolated with ether, and crystallised from a small amount of methyl alcohol in colourless prisms (1·2 g.), m. p. 82—84° (Found: Br, 18·8. $C_{20}H_{23}O_5Br$ requires Br, 18·9%).

2-*Bromo*-αδ-*bis*-3 : 4-*dimethoxyphenylbutane*.—The ketone (V) (0·5 g.) was gently boiled with amalgamated zinc (2·5 g.) and concentrated hydrochloric acid (2·5 c.c.) for 5 hours. The product, isolated with ether, crystallised from light petroleum (b. p. 40—60°) or methyl alcohol in colourless prisms (0·45 g.), m. p. 89—90° (Found: C, 58·5; H, 6·2; Br, 19·4. $C_{20}H_{25}O_4Br$ requires C, 58·7; H, 6·1; Br, 19·6%). This *compound*, treated with bromine (1 mol.) in acetic acid solution, gave the dibromo-derivative, m. p. 116—117°, mentioned below.

αδ-*Bis*-3 : 4-*dimethoxyphenylbutane* (VI; R = H).—A stream of hydrogen was passed for ½ hour through a boiling alcoholic solution (12 c.c.) of the above monobromo-compound (0·4 g.) in the presence of palladised charcoal (0·3 g. of 0·5%) and sodium hydroxide (0·6 c.c. of 8%). The mixture was filtered, the alcohol removed, and the residue crystallised from methyl alcohol; colourless slender prisms (0·25 g.), m. p. 90—91°, were obtained (Found: C, 72·6; H, 7·8. $C_{20}H_{26}O_4$ requires C, 72·7; H, 7·9%). αδ-*Bis*-2-*bromo*-4 : 5-*dimethoxyphenylbutane*, obtained by the action of bromine (2 mols.) on the above compound in acetic acid, crystallised from alcohol in colourless rectangular plates, m. p. 116—117° (Found: C, 49·3; H, 4·9; Br, 32·5. $C_{20}H_{24}O_4Br_2$ requires C, 49·2; H, 4·9; Br, 32·8%). αδ-*Bis*-2-*nitro*-4 : 5-*dimethoxyphenylbutane*, obtained by the action of nitric acid (2 mols.) in acetic acid solution, crystallised from acetic acid in pale yellow prisms, m. p. 184—185° (Found: C, 56·9; H, 5·7. $C_{20}H_{24}O_8N_2$ requires C, 57·1; H, 5·7%). It was reduced by means of zinc and hydrochloric acid to the corresponding diamino-compound, which gave a deep blue coloration with ferric chloride.

γ-(2-*Bromo*-4 : 5-*dimethoxyphenyl*)-αβ-*dimethylbutyric Acid*.—Bromine (5·1 g.) in acetic acid (10 c.c.) was added with cooling to a solution of γ-3 : 4-dimethoxyphenyl-αβ-dimethylbutyric acid (J., 1932, 1488) (8 g.) in acetic acid (15 c.c.). After 12 hours, water was added, and the product extracted with ether, washed thoroughly with water, dried, and the ether allowed to evaporate. The *bromo-acid* slowly separated; it crystallised from 70% acetic acid or light petroleum (b. p. 80—100°) in slender colourless prisms (6 g.), m. p. 104—105° (Found: C, 50·5; H, 5·7; Br, 24·1; *M*, 331. $C_{14}H_{19}O_4Br$ requires C, 50·7; H, 5·7; Br, 24·2%; *M*, 331). Attempts to condense the chloride (4·5 g.) of this acid with veratrole as described in the preparation of (V), gave an alkali-insoluble oil (3·4 g.), which yielded 1-keto-2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (0·9 g.), m. p. 135—137° after two crystallisations from methyl alcohol. The mother-liquors contained a viscous oil (2·2 g.) which would not crystallise or yield crystalline derivatives.

α-*Cyano*-αδ-*diphenylbutan*-β-*one* (VII; R = CN).—Phenylacetonitrile (6 g.) and methyl β-phenylpropionate (8·8 g.) were added to a suspension of potassium ethoxide (from molecular potassium, 2·8 g.) in benzene (60 c.c.), and the mixture boiled for 5 hours. Sodium hydroxide solution (100 c.c. of 0·5%) was added, the aqueous layer acidified, and the resulting oil isolated with ether and distilled. The *keto-nitrile* (VII; R = CN), b. p. 190—200°/0·4 mm., crystallised from light petroleum (b. p. 60—80°) in colourless needles (6·8 g.), m. p. 76—78° (Found: C, 82·0; H, 6·0. $C_{17}H_{15}ON$ requires C, 81·9; H, 6·0%). It dissolved in aqueous alkalis and gave a violet coloration with ferric chloride.

β-*Keto*-αδ-*diphenylvaleramide* (VII; R = CO·NH$_2$).—The above keto-nitrile (2·6 g.) was dissolved in glacial acetic acid (30 c.c.) and saturated with hydrogen chloride at 0°. After 40 hours, most of the acetic acid was removed under reduced pressure, and the residue treated with an equal volume of hot water. The *amide*, which separated on cooling, crystallised from 40% acetic acid in colourless needles (2·3 g.), m. p. 128° (Found: C, 76·4; H, 6·2. $C_{17}H_{17}O_2N$ requires C, 76·4; H, 6·3%). This amide was soluble in sodium hydroxide solution and gave a blue coloration with ferric chloride.

αδ-*Diphenylbutan*-β-*one* (VII; R = H).—The foregoing amide (3·1 g.) was boiled with concentrated hydrochloric acid (40 c.c.) for 12 hours. The product was extracted with ether, washed with dilute sodium hydroxide solution, and distilled; it boiled at 146—150°/0·2 mm., and crystallised from light petroleum (b. p. 40—45°) in long slender prisms (2·3 g.), m. p. 43—44° (Found: C, 86·1; H, 7·2. Calc. for $C_{16}H_{16}O$: C, 85·7; H, 7·2%). This ketone was insoluble in aqueous sodium hydroxide and gave no colour with ferric chloride. Tiffeneau, Orékhoff, and Lévy (*Bull. Soc. chim.*, 1931, **49**, 1845) prepared the same compound, m. p. 42—43°, by a different method during the course of this work.

αδ-*Diphenyl*-β-*methyl*-Δ^{α}-*butene* (VIII).—The above ketone (0·4 g.) in ether (5 c.c.) was gradually added to a solution of methylmagnesium iodide (from methyl iodide, 0·3 c.c., and magnesium, 0·09 g., in ether, 10 c.c.), and the mixture gently boiled for 1 hour. Decomposition with ammonium chloride solution yielded an oil, which was heated with 98% formic acid (5 c.c.) on the water-bath for 15 minutes. The product, isolated with ether, was an oil, which was treated with bromine (0·4 g.) in ether (5 c.c.). The *dibromide*, which slowly separated, crystallised from light petroleum (b. p. 60—80°) in colourless needles (0·4 g.), m. p. 91—92° (Found : Br, 41·8. $C_{17}H_{18}Br_2$ requires Br, 41·9%).

3 : 4-Dimethoxyphenylacetonitrile, m. p. 45—47°, was prepared in 40% yield from 3 : 4-dimethoxybenzaldehyde, essentially as described by Pfeiffer, Quehl, and Tappermann (*Ber.*, 1930, **63**, 1301), but the preparation of the oxime of 3 : 4-dimethoxyphenylpyruvic acid and its conversion into 3 : 4-dimethoxyphenylacetonitrile were carried by Edwards's method (J., 1926, 745) for a similar case. 2-*Bromo*-4 : 5-*dimethoxyphenylacetonitrile* was obtained in 90% yield by the addition of bromine (1 mol.) to an acetic acid solution of 3 : 4-dimethoxyphenylacetonitrile in the presence of sodium acetate. It crystallised from methyl alcohol in cream-coloured prisms, m. p. 90—91° (Found : Br, 31·3. $C_{10}H_{10}O_2NBr$ requires Br, 31·3%). The structure was settled by an independent synthesis from 2-bromo-4 : 5-dimethoxybenzaldehyde, in the course of which the following compounds were prepared : *azlactone* of 2-*bromo*-4 : 5-*dimethoxybenzaldehyde*, yellow needles, m. p. 206°, from acetic acid (Found : Br, 20·5. $C_{18}H_{14}O_4NBr$ requires Br, 20·6%) ; 2-*bromo*-4 : 5-*dimethoxyphenylpyruvic acid*, colourless prisms, m. p. 222—224°, from alcohol (Found : equiv., 308. $C_{11}H_{11}O_5Br$ requires equiv., 303), and its *oxime*, colourless needles, m. p. 172—173° (decomp.), from alcohol (Found : Br, 25·0. $C_{11}H_{12}O_5NBr$ requires Br, 25·2%).

β-3 : 4-*Dimethoxyphenyl*-α-*methylpropionic Acid*.—A mixture of 3 : 4-dimethoxybenzaldehyde (20 g.), ethyl α-bromopropionate (32 g.), zinc turnings (9·7 g.), and benzene (100 c.c.) was warmed gently until reaction commenced. When this had subsided, the mixture was boiled for ½ hour, cooled, and acidified with dilute sulphuric acid, the benzene layer separated and dried, and the solvent removed. The residue was distilled twice under diminished pressure, giving *ethyl* β-3 : 4-*dimethoxyphenyl*-α-*methylcrotonate*, b. p. 198—200°/15 mm., which crystallised from benzene–light petroleum (b. p. 60—80°) in colourless needles (29 g.), m. p. 97—98° (Found : C, 67·1; H, 7·0. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%). Hydrolysis with alcoholic potassium hydroxide yielded the acid, which crystallised from benzene in colourless needles, m. p. 140—141°. Tiemann and Kraaz (*Ber.*, 1882, **15**, 2072) give m. p. 140—141°. This acid (64 g.), dissolved in sodium hydroxide solution (2·5 l. of 0·64%), was reduced with sodium amalgam (3·74 kg. of 4%) at 80—90°, in the usual way. Acidification yielded β-(3 : 4-dimethoxyphenyl)-α-methylpropionic acid, which crystallised from ether–light petroleum (b. p. 40—60°) in colourless plates (59 g.), m. p. 58—59°. Tiemann and Kraaz (*loc. cit.*) give m. p. 58—59°. The *methyl* ester was a colourless viscous oil, b. p. 153—154°/0·4 mm. (Found : C, 65·4; H, 7·3. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·5%). β-2-*Bromo*-4 : 5-*dimethoxyphenyl*-α-*methylpropionic acid*, prepared by bromination of the above acid in acetic acid solution, crystallised from ether–light petroleum (b.p. 60—80°) in colourless needles, m.p. 94—95° (Found : Br, 26·1; equiv., 302. $C_{12}H_{15}O_4Br$ requires Br, 26·4%; equiv., 303). The position of the bromine atom was established by oxidation to 2-bromo-4 : 5-dimethoxybenzoic acid, m. p. 185°, with potassium permanganate in alkaline solution. The *methyl* ester was an oil, b. p. 162—164°/0·2 mm. (Found : Br, 25·4. $C_{13}H_{17}O_4Br$ requires Br, 25·2%).

β-*Keto*-αδ-*bis*-3 : 4-*dimethoxyphenyl*-γ-*methylvaleramide* (IX; R = $CO \cdot NH_2$).—Methyl β-3 : 4-dimethoxyphenyl-α-methylpropionate (15 g.) in benzene (40 c.c.) was added to 3 : 4-dimethoxyphenylacetonitrile (10 g.) and potassium ethoxide (from molecular potassium, 2·6 g.) in benzene (30 c.c.), and the mixture heated for 6 hours. The nitrile was isolated, after the same procedure as on p. 1426, as an oil, which gave a violet coloration with ferric chloride. It was dissolved in a mixture of acetic acid (40 c.c.) and concentrated hydrochloric acid (35 c.c.), saturated with hydrogen chloride at 0°, and kept at room temperature for 3 days. The solution was then diluted with water, extracted with ether, the extract washed thoroughly with water and dried, and the solvent removed. The residue, which slowly solidified, crystallised from benzene–light petroleum (b. p. 60—80°) in colourless prisms (5·9 g.), m. p. 130—131° (Found : C, 65·8; H, 6·5. $C_{22}H_{27}O_6N$ requires C, 65·9; H, 6·7%). This *amide* dissolved in sodium hydroxide solution and gave a deep purple coloration with ferric chloride.

3′ : 4′ : 5 : 6-*Tetramethoxy*-3-*benzyl*-2-*methylindene* (X).—The above amide (1 g.) was boiled with concentrated hydrochloric acid (15 c.c.) for 12 hours, the solution cooled, diluted with water, and extracted with ether, and the extract washed with dilute sodium hydroxide solution. The product crystallised from light petroleum (b. p. 80—100°) in colourless needles (0·5 g.), m. p. 115—117° (Found : C, 74·0; H, 7·1. $C_{21}H_{24}O_4$ requires C, 74·1; H, 7·1%). This *compound* was insoluble in alkali and gave no colour with ferric chloride. Catalytic reduction yielded a *dihydro*-derivative, which crystallised from light petroleum (b. p. 60—80°) in felted needles, m. p. 102—103° (Found : C, 73·6; H, 7·8. $C_{21}H_{26}O_4$ requires C, 73·7; H, 7·6%).

α-Cyano-αδ-bis-2-bromo-4 : 5-dimethoxyphenyl-γ-methylbutan-β-one (XI; R = CN), obtained similarly in 35% yield from 2-bromo-4 : 5-dimethoxyphenylacetonitrile and methyl β-2-bromo-4 : 5-dimethoxyphenyl-α-methylpropionate, crystallised from benzene–light petroleum (b. p. 60—80°) in colourless needles, m. p. 130—131° (Found : Br, 29·7. $C_{22}H_{23}O_5NBr_2$ requires Br, 29·6%). Hydrolysis with a cold mixture of acetic and hydrochloric acids yielded *β-keto-αδ-bis-2-bromo-4 : 5-dimethoxyphenyl-γ-methylvaleramide* (XI; R = CO•NH$_2$), which crystallised from benzene–light petroleum (b. p. 60—80°) in small nodules, m. p. 174—175° (Found : Br, 28·5. $C_{22}H_{25}O_6NBr_2$ requires Br, 28·6%). Both nitrile and amide, described above, dissolved in aqueous sodium hydroxide, but they gave no colour with ferric chloride. *αδ-Bis-2-bromo-4 : 5-dimethoxyphenyl-γ-methylbutan-β-one* (XI; R = H), obtained by the action of boiling concentrated hydrochloric acid on the above amide, crystallised from methyl alcohol in slender white needles, m. p. 105—106° (Found : C, 49·1; H, 4·9; Br, 30·6. $C_{21}H_{24}O_5Br_2$ requires C, 48·8; H, 4·7; Br, 31·0%).

αδ-Bis-3 : 4-dimethoxyphenyl-γ-methylbutan-β-one (IX; R = H).—The amide (IX; R = CO•NH$_2$) (6 g.) was boiled with 20% sodium hydroxide solution (35 c.c.) for 4 hours, and after cooling and dilution with water, the product was extracted with ether. The *ketone* (IX; R = H) (2·7 g.) was obtained as an oil, b. p. 226—228°/0·2 mm. (Found : C, 70·2; H, 7·5. $C_{21}H_{26}O_5$ requires C, 70·4; H, 7·3%), which gave no colour with ferric chloride. The *dinitro*-compound, prepared by nitrating the above ketone in acetic acid solution, crystallised from 90% acetic acid in buff-coloured needles, m. p. 175—176° (Found : C, 56·1; H, 5·5. $C_{21}H_{24}O_9N_2$ requires C, 56·2; H, 5·3%). The dinitro-compound was reduced with zinc dust and hydrochloric acid in alcoholic solution. The mixture was diluted with water and filtered; the filtrate gave a deep blue coloration with ferric chloride. The same dinitro-compound was obtained by nitrating the oil (1·3 g.), b. p. 226—230°/0·2 mm., obtained by boiling the amide (IX; R = CO•NH$_2$) (2 g.) with 10% hydrochloric acid (25 c.c.) for 2 hours.

dl-*Guaiaretic Acid Dimethyl Ether* (I; R = Me).—An ice-cold ethereal solution of methylmagnesium iodide (from magnesium, 0·5 g., and methyl iodide, 3·5 g., in ether, 30 c.c.) was treated with an ethereal solution (20 c.c.) of αδ-bis-3 : 4-dimethoxyphenyl-γ-methylbutan-β-one (IX; R = H) (2·0 g.). After standing for 1 hour, the mixture was boiled for ½ hour and decomposed with ammonium chloride solution. The oily carbinol was heated with potassium hydrogen sulphate (2 g.) at 150° for ½ hour, the product extracted with ether, washed with dilute sodium hydroxide solution and dried, and the solvent removed. The residue (A) crystallised on standing, and recrystallised from methyl alcohol in colourless plates (0·4 g.), m. p. 112—113° (Found : C, 74·3; H, 8·0. $C_{22}H_{28}O_4$ requires C, 74·2; H, 7·9%). This compound rapidly absorbed bromine in chloroform solution, and decolorised an acetone solution of potassium permanganate. A similar reaction was carried out with the crude ketone obtained by the hydrolysis of the amide (IX; R = CO•NH$_2$) with dilute hydrochloric acid, but the residue (A) could not be obtained crystalline.

Dehydroguaiaretic Dimethyl Ether (II).—Hübl's iodine solution (containing iodine, 2 g.) was added to a solution of *dl*-guaiaretic acid dimethyl ether (1 g.) in warm alcohol. After standing at room temperature for 3 days, the crystalline deposit was collected, washed with potassium iodide solution, and recrystallised from acetic acid. The ether (0·6 g.) was obtained in colourless plates, m. p. 178—179° (S., L., and I., *loc. cit.*, give 178·5—179°) (Found : C, 74·8; H, 6·9. Calc. for $C_{22}H_{24}O_4$: C, 75·0; H, 6·8%). The alcohol and acetic acid mother-liquors yielded a further small crop of (II); no dihydroguaiaretic acid dimethyl ether could be isolated, either as such or in the form of its dibromo-derivative (see below).

dl-*Dihydroguaiaretic Acid Dimethyl Ether* (VI; R = Me).—A solution of *dl*-guaiaretic acid dimethyl ether (1 g.) in alcohol (20 c.c.) was reduced with hydrogen in the presence of palladised charcoal (1 g. of 0·5%). The catalyst was removed, and the filtrate concentrated to a small bulk and cooled. The crystals which separated were collected and recrystallised from formic acid; colourless needles (0·8 g.), m. p. 101—102°, were obtained (Found : C, 73·7; H, 8·4. Calc. for $C_{22}H_{30}O_4$: C, 73·7; H, 8·4%), identical with the natural material (see p. 1425). The following derivatives of the synthetic compound were prepared by methods described by Schroeter, Lichtenstadt, and Irineu (*loc. cit.*) : dibromo-derivative, colourless needles from methyl alcohol, m. p. 131—132° (Found : Br, 31·2. Calc. for $C_{22}H_{28}O_4Br_2$: Br, 31·0%), dinitro-derivative, stout prisms from formic acid, m. p. 151—152° (Found : N, 6·2. Calc. for $C_{22}H_{28}O_8N_2$: N, 6·2%), αδ-bis-3 : 4-dihydroxyphenyl-βγ-dimethylbutane (norhydroguaiaretic acid), small prisms from aqueous acetic acid, m. p. 184—185° (Found : C, 71·8; H, 7·3. Calc. for $C_{18}H_{22}O_4$:

C, 71·5; H, 7·2%). No depression in m. p. was observed when these derivatives were mixed with the corresponding derivatives prepared from natural dihydroguaiaretic acid dimethyl ether.

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