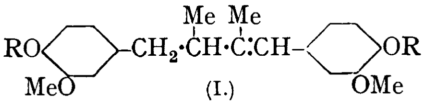
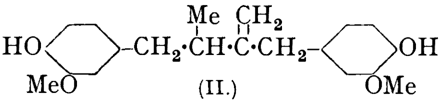
26. *The Constituents of Guaiacum Resin. Part III. Synthesis of* dl-*Guaiaretic Acid Diethyl Ether.*

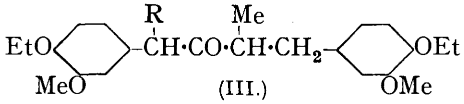
By Robert D. Haworth and Thomas Richardson.

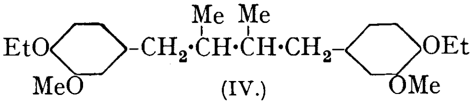
The synthesis of guaiaretic acid dimethyl ether (J., 1934, 1423) confirmed the main features of the formula (I; R = H) first suggested for guaiaretic acid by Schroeter, Lichtenstadt, and Irineu (*Ber.*, 1918, **51**, 1587), but the positions of the ethylenic linkage and the phenolic hydroxyl groups remained undetermined. Although the optical activity of guaiaretic acid can be explained by either formula (I; R = H) or (II), the latter fails to account for the facile transformation of the acid into derivatives of 1-phenylnaphthalene. Further, (II) can be discarded, as it has now been shown that neither formaldehyde nor formic acid is obtained by ozonisation of *l*-guaiaretic acid dimethyl ether in chloroform solution. The remaining problem, concerning the position of the two phenolic hydroxyl groups, has now been settled in favour of formula (I; R = H) by an unambiguous synthesis of guaiaretic acid diethyl ether (I; R = Et).


(I.)


(II.)

β-3-*Methoxy*-4-*ethoxyphenyl*-α-*methylcrotonic acid*, prepared from 3-methoxy-4-ethoxybenzaldehyde and ethyl α-bromopropionate, was reduced to β-3-*methoxy*-4-*ethoxyphenyl*-α-*methylpropionic acid.* The methyl ester of this acid and 3-*methoxy*-4-*ethoxyphenylacetonitrile*, obtained by the action of acetic anhydride on the oxime of 3-methoxy-4-ethoxyphenylpyruvic acid (Barger, Eisenbrand, Eisenbrand, and Schittler, *Ber.*, 1933, **66**, 453), condensed in the presence of potassium ethoxide to give an oily cyano-ketone, which was hydrolysed with concentrated hydrochloric acid in cold acetic acid solution to β-*keto*-αδ-*bis*-(3-*methoxy*-4-*ethoxyphenyl*)-γ-*methylvaleramide* (III; R = CO·NH$_2$). This amide was


(III.)


(IV.)

converted by alkaline hydrolysis into αδ-*bis*-(3-*methoxy*-4-*ethoxyphenyl*)-γ-*methylbutan*-β-*one* (III; R = H), which, in contrast to the corresponding tetramethoxy-ketone described in the previous memoir (*loc. cit.*, p. 1428), was readily obtained in the crystalline condition. The ketone (III; R = H) reacted with methylmagnesium iodide, yielding a carbinol, which was dehydrated with potassium hydrogen sulphate to dl-*guaiaretic acid diethyl ether*, m. p. 103—104° (I; R = Et). Catalytic reduction afforded optically inactive *dihydroguaiaretic acid diethyl ether*, m. p. 98—99° (IV). *l*-Guaiaretic acid, obtained from guaiacum resin as described by Schroeter, Lichtenstadt, and Irineu (*loc. cit.*), was ethylated to give l-*guaiaretic acid diethyl ether*, which was reduced catalytically to an optically inactive dihydro-derivative, m. p. 98—99°, identical with the synthetic product (IV) mentioned above. The identity was also confirmed by the preparation of the *dibromo*- and the *dinitro*-derivatives.

EXPERIMENTAL.

3-*Methoxy*-4-*ethoxyphenylacetonitrile*.—A solution of 3-methoxy-4-ethoxyphenylpyruvic acid (40 g.) and hydroxylamine hydrochloride (15 g.) in 8% sodium hydroxide solution (250 c.c.) was heated at 100° for 1·5 hours. Acidification of the cold solution precipitated the oxime (35 g.), which was dried and heated with acetic anhydride (140 g.) at 100° for 2 hours. The anhydride was removed under reduced pressure and the residue was dissolved in ether, washed with sodium bicarbonate solution, dried, recovered, and distilled. The *nitrile*, b. p. 156—158°/0·4 mm., crystallised from methyl alcohol in pale yellow prisms (18 g.), m. p. 53—54° (Found: C, 69·3; H, 6·7. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·9%).

β-3-*Methoxy*-4-*ethoxyphenyl*-α-*methylcrotonic Acid*.—A solution of 3-methoxy-4-ethoxybenzaldehyde (40 g.) in benzene (120 c.c.) was heated on the water-bath with zinc filings (17 g.) and ethyl α-bromopropionate (56 g.). After the initial violent reaction had subsided, the heating was continued for ½ hour. The mixture was decomposed with dilute sulphuric acid and the product, isolated with benzene, was heated with potassium hydrogen sulphate (20 g.) at 180° for ½ hour. The *ethyl* ester was extracted with ether and distilled; it boiled at 195—200°/15 mm., and crystallised from benzene–light petroleum in stout prisms, m. p. 58—60° (Found: C, 67·9; H, 7·8. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%). Hydrolysis with methyl-alcoholic potassium hydroxide yielded the *acid*, which crystallised from benzene in colourless needles (28 g.), m. p. 127—128° (Found: C, 66·0; H, 6·8. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

β-3-*Methoxy*-4-*ethoxyphenyl*-α-*methylpropionic acid*, obtained in 80% yield by reduction of the above crotonic acid with sodium amalgam, crystallised from ether–light petroleum in colourless plates, m. p. 63—64° (Found: equiv., 240. $C_{13}H_{18}O_4$ requires equiv., 238). The methyl ester, prepared by the Fischer–Speier method, was a colourless oil, b. p. 158—160°/0·3 mm.

β-*Keto*-αδ-*bis*-(3-*methoxy*-4-*ethoxyphenyl*))-γ-*methylvaleramide* (III; R = CO·NH$_2$).—A solution of methyl β-(3-methoxy-4-ethoxyphenyl)-α-methylpropionate (8·6 g.) and 3-methoxy-4-ethoxyphenylacetonitrile (6 g.) in benzene (120 c.c.) was added to a suspension of potassium ethoxide (prepared from 2·1 g. of potassium) in benzene (20 c.c.). After heating on the water-bath for 6 hours, the cyano-ketone was extracted with 1% sodium hydroxide solution, recovered, and isolated with ether as an oil, which did not crystallise and gave a transient purple colour with ferric chloride. The crude cyano-ketone (7·2 g.), dissolved in a mixture of glacial acetic acid (10 c.c.) and concentrated hydrochloric acid (30 c.c.), was saturated with hydrogen chloride at 0° and kept for 3 days. The mixture was diluted with water and extracted with ether; the extract was washed several times with water and then with dilute sodium bicarbonate solution, dried, and the solvent removed. The residual *amide* (III; R = CO·NH$_2$) solidified on cooling and crystallised from benzene–light petroleum in colourless plates (3·3 g.), m. p. 114—115° (Found: C, 67·1; H, 7·2. $C_{24}H_{31}O_6N$ requires C, 67·1; H, 7·3%). The amide was soluble in sodium hydroxide solution and gave a violet colour with ferric chloride.

αδ-*Bis*-(3-*methoxy*-4-*ethoxyphenyl*)-α-*methylbutan*-β-*one* (III; R = H).—The above amide

(6 g.) was boiled with 20% sodium hydroxide solution (35 c.c.) for 4 hours. The alkali-insoluble product, isolated with ether, boiled at 230—235°/0·3 mm., and crystallised from ether–light petroleum in colourless prisms (1·5 g.), m. p. 57—58° (Found : C, 71·3; H, 8·0. $C_{23}H_{30}O_5$ requires C, 71·5; H, 7·8%). The *dinitro*-derivative crystallised from acetic acid in cream needles, m. p. 133—134° (Found : C, 58·2; H, 5·7. $C_{23}H_{28}O_9N_2$ requires C, 58·0; H, 5·9%), and reduction with zinc dust and hydrochloric acid yielded an amine which gave a blue colour with ferric chloride.

dl-*Guaiaretic Acid Diethyl Ether* (I; R = Et).—A solution of methylmagnesium iodide (from 0·3 g. of magnesium and 0·8 c.c. of methyl iodide) in ether (15 c.c.) was gradually added to an ice-cold solution of the above ketone (III; R = H) (1 g.) in ether (15 c.c.). After 1 hour, the mixture was heated on the water-bath for ½ hour, and decomposed with ammonium chloride solution. The carbinol (0·9 g.), isolated with ether, was heated with potassium hydrogen sulphate (1 g.) at 150° for 1 hour. The product was extracted with ether and washed first with water and then with dilute sodium hydroxide solution; removal of the solvent gave an oil, which rapidly solidified and then crystallised from methyl alcohol in colourless prisms (0·35 g.), m. p. 103—104° (Found : C, 74·8; H, 8·4. $C_{24}H_{32}O_4$ requires C, 75·0; H, 8·4%).

l-*Guaiaretic Acid Diethyl Ether* (I; R = Et).—Ethyl iodide (4 g.) was gradually added to a boiling suspension of the potassium salt, obtained by adding a solution of potassium hydroxide (1·2 g.) in 80% alcohol (16 c.c.) to *l*-guaiaretic acid (1·5 g.) in alcohol (5 c.c.). After 3 hours, the alcohol was removed, the residue diluted with water, and the solid (1·7 g.) collected. Three crystallisations from methyl alcohol yielded the *diethyl* ether (1·1 g.) as colourless prisms, m. p. 95—96°; $[\alpha]_D^{19°}$ – 48·0° in ethyl alcohol (c = 0·835) (Found : C, 74·7; H, 8·5. $C_{24}H_{32}O_4$ requires C, 75·0; H, 8·4%).

Optically Inactive Dihydroguaiaretic Acid Diethyl Ether (IV).—A rapid stream of hydrogen was passed for 3 hours through a boiling alcoholic solution (15 c.c.) of either *l*- or *dl*-guaiaretic acid diethyl ether (1 g.) in presence of palladised charcoal (1·0 g. of 0·5%). The liquid was filtered and evaporated, leaving a residue, which crystallised from methyl alcohol in colourless prisms, m. p. 98—99° (Found : C, 74·7; H, 8·4. $C_{24}H_{34}O_4$ requires C, 74·6; H, 8·9%). No depression in m. p. was observed when specimens prepared from the two sources were mixed. The compound was optically inactive in alcohol or chloroform solution. The *dibromo*-derivative, obtained by the action of bromine (2 mols.) in acetic acid solution, crystallised from acetic acid in colourless needles, m. p. 134—135° (Found : Br, 29·5. $C_{24}H_{32}O_4Br_2$ requires Br, 29·4%). The *dinitro*-derivative, prepared by the action of concentrated nitric acid (2 mols.) in acetic acid solution, crystallised from acetic acid in cream-coloured prisms, m. p. 111—112° (Found : C, 60·5; H, 6·8. $C_{24}H_{32}O_8N_2$ requires C, 60·8; H, 6·7%).

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