108. *Chemical Investigation of* Wedelia calendulacea. *Part II.*[1] *The Position of the Methoxyl Group in Wedelolactone.*

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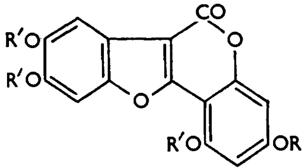
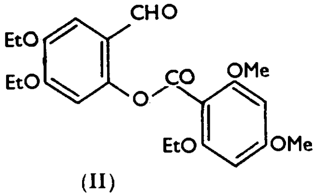
Wedelolactone is shown to be the lactone (Ia) of 5 : 6-dihydroxy-2-(2 : 6-dihydroxy-4-methoxyphenyl)benzofuran-3-carboxylic acid.

Tri-*O*-methylwedelolactone has been shown [1] to have the structure (I). Evidence is now presented to show that wedelolactone has structure (Ia).

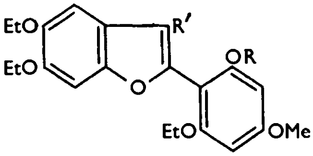
Ethylation of wedelolactone gave tri-*O*-ethylwedelolactone which was hydrolysed to tri-*O*-ethylwedelic acid which on methylation yielded methyl tri-*O*-ethyl-*O*-methylwedelate. Hydrolysis of the ester gave tri-*O*-ethyl-*O*-methylwedelic acid which lost carbon dioxide above its melting point, to yield a compound, $C_{22}H_{26}O_6$. Ozonolysis of this gave a compound $C_{22}H_{26}O_8$, hydrolysed by alcoholic alkali into a phenolic aldehyde and an acid. The phenol was identified as 4 : 5-diethoxy-2-hydroxybenzaldehyde by analysis and comparison of its ethyl ether with a specimen made by formylation of 1 : 2 : 4-triethoxybenzene. The acidic component was decarboxylated during isolation to 1-ethoxy-3 : 5-dimethoxybenzene and was thus 2-ethoxy-4 : 6-dimethoxy- or 2 : 6-dimethoxy-4-ethoxybenzoic acid. The ozonolysis product was reduced by lithium aluminium hydride to a mixture of 2-ethoxy-4 : 6-dimethoxybenzyl alcohol (different from 2 : 6-dimethoxy-4-ethoxybenzyl alcohol from which it differed in melting point only slightly), and a phenolic alcohol whose dibenzoate had the analysis expected for 2-benzoyloxy-4 : 5-diethoxybenzyl benzoate.



(I) R = R' = Me
(Ia) R = Me, R' = H
(Ib) R = Me, R' = Et



(II)



(III) R = Me, R' = H
(IIIa) R = Me, R' = CO_2H
(IIIb) R = H, R' = CO_2H

The degradations show that the ozonolysis product is 4 : 5-diethoxy-2-(2-ethoxy-4 : 6-dimethoxybenzoyloxy)benzaldehyde (II) and that the decarboxylation product $C_{22}H_{26}O_6$ is 5 : 6-diethoxy-2-(2-ethoxy-4 : 6-dimethoxyphenyl)benzofuran (III). Tri-*O*-ethyl-*O*-methylwedelic acid and tri-*O*-ethylwedelic acid must have structures (IIIa) and (IIIb) respectively. Tri-*O*-ethylwedelolactone should therefore be represented by (Ib), and wedelolactone has the structure (Ia).

Experimental

*Tri-*O*-ethylwedelolactone.*—Wedelolactone (4 g.) with diethyl sulphate (25 ml.) and potassium carbonate (40 g.) in boiling dry acetone (100 ml.) (8 hr.) gave *tri-*O*-ethylwedelolactone* (2·8 g.) needles (from acetic acid–alcohol or acetone–alcohol), m. p. 200—201° (Found: C, 65·9; H, 6·0. $C_{22}H_{22}O_7$ requires C, 66·3; H, 5·5%). The ether (0·65 g.) was also obtained by refluxing the lactone (1 g.) with ethyl iodide (10 ml.) and potassium carbonate (15 g.) in acetone (30 ml.).

Ozonolysis of the ether (0·5 g.) in chloroform (25 ml.) at 0° gave only resins.

*Tri-*O*-ethylwedelic Acid.*—A suspension of the lactone (2·8 g.) in alcohol (100 ml.) containing

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[1] Govindachari, Nagarajan, and Pai, *J.*, 1956, 629.

potassium hydroxide (10 g.) was refluxed for 4 hr. The solvent was distilled off and water added to the syrupy residue. The solution was filtered from amorphous material and acidified with strong cooling. *Tri-O-ethylwedelic acid* (2·8 g.) so obtained crystallised from dilute methanol as colourless needles which lost water at 182° and melted at 195—197° (Found: C, 64·2; H, 5·7. $C_{22}H_{24}O_8$ requires C, 63·5; H, 5·8%). The acid (20 mg.) when heated at 220—240° for 2 hr. and crystallised from alcoholic acetic acid gave tri-*O*-ethylwedelolactone, m. p. and mixed m. p. 200—201°.

Methyl Tri-O-ethyl-O-methylwedelate.—The acid (2 g.), methyl iodide (10 ml.), potassium carbonate (10 g.), and acetone (50 ml.) were refluxed for 8 hr., affording, after fractional crystallisation from methanol, small amounts (0·2 g.) of impure tri-*O*-ethylwedelolactone and *methyl tri-O-ethyl-O-methylwedelate* (1·5 g.), m. p. 125—127°. Recrystallisation from methanol gave colourless cubes, m. p. 127—128° (Found: C, 65·2; H, 6·0. $C_{24}H_{28}O_8$ requires C, 64·9; H, 6·3%).

The methyl ester (1·4 g.) was hydrolysed by potassium hydroxide (4·5 g.) in boiling water (20 ml.) and alcohol (20 ml.) in 3 hr. to *tri-O-ethyl-O-methylwedelic acid* (1·4 g.), needles (from methanol), 183—185° (gas evolution) (Found: C, 64·2; H, 6·0. $C_{23}H_{26}O_8$ requires C, 64·2; H, 6·0%). Treatment of the acid with ethereal diazomethane gave the methyl ester, m. p. and mixed m. p. 126—128°.

Decarboxylation of Tri-O-ethyl-O-methylwedelic Acid.—The acid (1·4 g.) was heated at 220—240° for 3 hr. and the product sublimed *in vacuo* at 180°/(0·1—0·5 mm.). The sublimate on crystallisation from light petroleum (b. p. 60—80°) gave 5 : *6-diethoxy-2-(2-ethoxy-4 : 6-dimethoxyphenyl)benzofuran* (0·75 g.), cubes, m. p. 92—94° (Found: C, 68·3; H, 7·0. $C_{22}H_{26}O_6$ requires C, 68·4; H, 6·7%).

Ozonolysis of 5 : 6-Diethoxy-2-(2-ethoxy-4 : 6-dimethoxyphenyl)benzofuran.—A solution of the decarboxy-compound (0·6 g.) in chloroform (30 ml.) was treated with ozone (0·11 g.) at 0° during 3·5 hr. The solvent was evaporated and the residual ozonide heated on a water-bath with water (100 ml.), zinc dust (0·2 g.), and a few crystals each of silver nitrate and quinol for 1 hr. The solution was cooled, shaken with benzene, filtered, and acidified. The benzene layer was separated and the aqueous layer extracted repeatedly with benzene. The combined extracts were washed with dilute alkali and then with water, and dried (Na_2SO_4). Evaporation and crystallisation of the residue from methanol gave needles of 4 : *5-diethoxy-2-(2-ethoxy-4 : 6-dimethoxybenzoyloxy)benzaldehyde* (0·2 g.), m. p. 131—133°, raised to 133—134° by a second crystallisation (Found: C, 62·8; H, 6·7. $C_{22}H_{26}O_8$ requires C, 63·2; H, 6·2%), which afforded a 2 : *4-dinitrophenylhydrazone*, orange needles (from acetic acid), m. p. 256—258° (Found: C, 56·3; H, 5·2. $C_{28}H_{30}O_{11}N_4$ requires C, 56·2; H, 5·0%).

Hydrolysis of 4 : 5-Diethoxy-2-(2-ethoxy-4 : 6-dimethoxybenzoyloxy)benzaldehyde.—A solution of the above product (0·55 g.) in ethanol (25 ml.) containing potassium hydroxide (3 g.) was left at 30° for 6 hr. The solvent was then evaporated *in vacuo*, and the residue taken up in water and extracted with ether. The aqueous layer was saturated with carbon dioxide and extracted with ether. The dried ethereal layer on evaporation gave 4 : *5-diethoxy-2-hydroxybenzaldehyde* (0·28 g.), crystallising from ice-cold light petroleum (b. p. 40—60°) as needles, m. p. 52—54° (Found: C, 63·4; H, 6·5. $C_{11}H_{14}O_4$ requires C, 62·9; H, 6·7%), giving a dark green colour with ferric chloride changing to brown on dilution. The aldehyde (60 mg.), ethylated with ethyl iodide (1 ml.) and potassium carbonate (2 g.) in acetone (10 ml.), gave 2 : 4 : *5-triethoxybenzaldehyde*, needles [from light petroleum (b. p. 40—60°)], m. p. 94—95° alone or mixed with 2 : 4 : 5-triethoxybenzaldehyde (see below) (Found: C, 65·2; H, 7·5. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%). The 2 : 4-dinitrophenylhydrazone, chocolate brown needles (from acetic acid), m. p. 200—201°, showed no depression on admixture with a synthetic specimen.

The bicarbonate extract from the hydrolysis was acidified and extracted with ether. Evaporation of the ether yielded a neutral oil (0·1 g.), which solidified. Crystallisation from ice-cold light petroleum (b. p. 40—60°) gave colourless cubes of *1-ethoxy-3 : 5-dimethoxybenzene*, m. p. 42—43° (Found: C, 66·1; H, 7·7. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%).

Lithium Aluminium Hydride Reduction of 4 : 5-Diethoxy-2-(2-ethoxy-4 : 6-dimethoxybenzoyloxy)benzaldehyde.—The aldehyde (0·3 g.) in ether (30 ml.) and tetrahydrofuran (10 ml.) was added to a stirred suspension of lithium aluminium hydride (1 g.) in ether (50 ml.) during 30 min. and left overnight. After decomposition with water, the ether–tetrahydrofuran layer was decanted from the sludge, which was then extracted thoroughly with ether. The combined ether extracts were washed with alkali and dried. Evaporation left a solid (0·13 g.), which on crystallisation from light petroleum (b. p. 40—60°) afforded 2-*ethoxy*-4 : 6-*dimethoxybenzyl alcohol*, needles, m. p. 76—77° (Found: C, 62·2; H, 7·2. $C_{11}H_{16}O_4$ requires C, 62·3; H, 7·6%), mixed m. p. 75—77° with a synthetic specimen (see below). Admixture with 4-ethoxy-2 : 6-dimethoxybenzyl alcohol (see below) lowered the m. p. to 55—60°.

The sludge in the reduction was dissolved in excess of dilute sulphuric acid and extracted thoroughly with ether. The dried ether layer on evaporation left 4 : 5-diethoxy-2-hydroxybenzyl alcohol (0·14 g.) as a gum which with benzoyl chloride and pyridine at 100° gave a *dibenzoate*, m. p. 159—160° (from benzene–methanol) (Found: C, 72·0; H, 6·2. $C_{25}H_{24}O_6$ requires C, 71·4; H, 5·7%).

2 : 4 : 5-*Triethoxybenzaldehyde*.—1 : 2 : 4-Trihydroxybenzene [2] (4 g.), ethyl iodide (15 ml.), and potassium carbonate (20 g.) were refluxed in dry acetone (50 ml.) for 6 hr. Recovery and distillation gave 1 : 2 : 4-triethoxybenzene (4·9 g.), b. p. 128°/15 mm., needles, m. p. 34° (Will *et al.*[3] give 34°).

1 : 2 : 4-Triethoxybenzene (2 g.), dimethylformamide (1 g.), and phosphoryl chloride (2 ml.) were heated at 100° for 6 hr., then treated with saturated aqueous sodium acetate (20 g.) and refluxed for 30 min. On cooling, 2 : 4 : 5-*triethoxybenzaldehyde* crystallised as fibrous needles, was filtered off, and washed with water. Recrystallisation from light petroleum (b. p. 40—60°) gave needles (1·6 g.), m. p. 95° (Found: C, 65·0; H, 7·2%), which afforded a 2 : 4-*dinitrophenylhydrazone*, chocolate-brown needles (from acetic acid), m. p. 200—201° (Found: C, 54·7; H, 5·5. $C_{19}H_{22}O_7N_4$ requires C, 54·5; H, 5·3%).

Methyl 2-*Ethoxy*-4 : 6-*dimethoxybenzoate*.—Methyl 2-hydroxy-4 : 6-dimethoxybenzoate [4] (2 g.), ethyl iodide (10 g.), and potassium carbonate (10 g.) in dry acetone (20 ml.) were refluxed for 6 hr. Crystallisation of the product from 20% alcohol gave *methyl* 4 : 6-*dimethoxy*-2-*ethoxybenzoate* (2·3 g.), needles, m. p. 56° (Found: C, 60·2; H, 6·7. $C_{12}H_{16}O_5$ requires C, 60·0; H, 6·7%).

2-*Ethoxy*-4 : 6-*dimethoxybenzyl Alcohol*.—The foregoing ester (1·6 g.) in ether (50 ml.) was added to a stirred suspension of lithium aluminium hydride (1 g.) in ether (60 ml.). Next morning the mixture was decomposed with water. The ether was decanted, dried (Na_2SO_4), and evaporated. Crystallisation of the residue (1·2 g.) from light petroleum (b. p. 40—60°) gave 2-*ethoxy*-4 : 6-*dimethoxybenzyl alcohol*, needles, m. p. 76—77° (Found: C, 62·7; H, 7·1%).

4-*Ethoxy*-2 : 6-*dimethoxybenzyl Alcohol*.—Ethylation of methyl 4-hydroxy-2 : 6-dimethoxybenzoate [5] (0·2 g.) with ethyl iodide (3 ml.) and potassium carbonate (2 g.) in acetone (10 ml.) gave methyl 4-ethoxy-2 : 6-dimethoxybenzoate as a viscous oil (0·15 g.). Reduction with lithium aluminium hydride (0·5 g.) in ether (10 ml.) gave 4-*ethoxy*-2 : 6-*dimethoxybenzyl alcohol*, needles (0·1 g.), m. p. 70—71° [from light petroleum (b. p. 40—60°)] (Found: C, 62·4; H, 7·4%).

Both the alcohols resinified when kept or heated for a short time.

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[2] Robinson and Healey, *J.*, 1934, 1625.
[3] Will and Pukall, *Ber.*, 1887, **20**, 1133.
[4] Holmes, White, and Wilson, *J.*, 1950, 2810.
[5] Fischer and Pfeffer, *Annalen*, 1912, **389**, 198.