126. *Chemical Examination of* Wedelia calendulacea. *Part I. Structure of Wedelolactone.*

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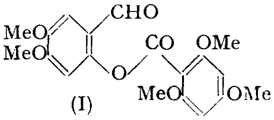
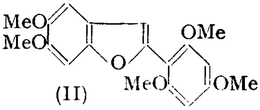
A new lactone, wedelolactone, has been isolated from *Wedelia calendulacea.* Its trimethyl ether is shown to be the lactone of 2-(2-hydroxy-4 : 6-dimethoxyphenyl)-5 : 6-dimethoxybenzofuran-3-carboxylic acid.

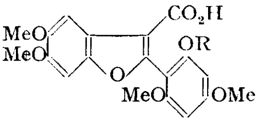
From *Wedelia calendulacea* (natural order Compositæ) we have isolated a lactone $C_{16}H_{10}O_7$, named wedelolactone, which contains one methoxyl group, forms a triacetate and a tribenzoate, and has an absorption band at 1707 cm.$^{-1}$ characteristic of an unsaturated δ-lactone. Complete methylation with dimethyl sulphate and potassium carbonate in acetone gave tri-*O*-methylwedelolactone, $C_{19}H_{16}O_7$; on hydrolysis this yielded tri-*O*-methylwedelic acid, $C_{19}H_{18}O_8$, which gave a blue colour with Folin–Denis reagent and was converted back into tri-*O*-methylwedelolactone when heated alone or refluxed with alcoholic hydrogen chloride. The acid with ethereal diazomethane gave methyl tetra-*O*-methylwedelate, $C_{21}H_{22}O_8$, which showed a negative Folin–Denis test and had an ester-carbonyl absorption at 1716 cm.$^{-1}$, indicating its probable aromatic nature. Hydrolysis of this ester with alcoholic potassium hydroxide gave tetra-*O*-methylwedelic acid, $C_{20}H_{20}O_8$, which was readily decarboxylated at 240—260°.

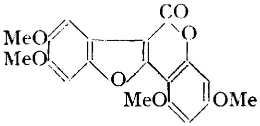
Ozonolysis of the decarboxylation product, $C_{19}H_{20}O_6$, in chloroform gave an ozonide which was decomposed to a crystalline aldehyde, $C_{19}H_{20}O_8$, showing absorption bands at 1675 (aromatic aldehyde) and 1753 cm.$^{-1}$ (phenol ester). Alkaline hydrolysis of the ozonolysis product furnished 6-hydroxyveratraldehyde and 2 : 4 : 6-trimethoxybenzoic acid. (It may be noted that 6-hydroxyveratraldehyde forms the dimedone derivative with direct elimination of two molecules of water, which seems to be a characteristic of *o*-hydroxybenzaldehydes.[1])

From the above experiments it is clear that the ozonolysis product is 6-(2 : 4 : 6-trimethoxybenzoyloxy)veratraldehyde (I), and that the product, $C_{19}H_{20}O_6$, obtained by decarboxylation of tetra-*O*-methylwedelic acid is 5 : 6-dimethoxy-2-(2 : 4 : 6-trimethoxyphenyl)benzofuran (II). Tetra- and tri-*O*-methylwedelic acid must be represented by (III) and (III*a*) respectively. Tri-*O*-methylwedelolactone can therefore be assigned structure (IV).


(I)


(II)


(III) : R = Me
(III*a*) : R = H


(IV)

Work is in progress with a view to locating the lone methoxy-group in wedelolactone.

EXPERIMENTAL

Ultraviolet absorption spectra were measured for absolute ethanol solutions with a Beckman Model DUV Spectrophotometer. Analyses are by Mr. S. Selvavinayagam.

Extraction of Wedelia calendulacea.—Fresh green leaves of the plant (3 kg.) were extracted continuously with hot 90% alcohol containing 2% of acetic acid until the extract was no longer coloured. The extract was then concentrated until separation of solid material began. After cooling and removal of a considerable amount of chlorophyll and wax that had separated, the filtrate was concentrated *in vacuo* to 1—1·5 l. and extracted repeatedly with ether until the latter was colourless. The combined ether extracts were washed with water, dried (Na_2SO_4), and evaporated. The residual green solid was washed with a little ether, to give *wedelolactone* (0·5 g. per kg. of fresh leaves). Two crystallisations from methanol gave greenish-yellow needles, m. p. 327—330° (decomp. from 280°) (Found : C, 61·2, 61·6; H, 3·3, 3·2; OMe, 8·5. $C_{16}H_{10}O_7$ requires C, 61·2; H, 3·2; 1OMe, 9·9%). The lactone is sparingly soluble in ether, methanol, ethanol, benzene, and chloroform, but readily soluble in warm pyridine; an alcoholic solution gives a dark green colour with ferric chloride. The *triacetate*, made by use of acetic anhydride in pyridine at 100°, crystallised from acetic acid in needles, m. p. 235—237° (Found : C, 60·3; H, 3·8. $C_{22}H_{16}O_{10}$ requires C, 60·0; H, 3·6%). The *tribenzoate*, prepared by use of benzoyl chloride in alkali, on crystallisation from 2-ethoxyethanol, melted at 267—269° (Found : C, 71·2; H, 3·9. $C_{37}H_{22}O_{10}$ requires C, 70·9; H, 3·5%).

*Tri-*O*-methylwedelolactone*.—Wedelolactone (2 g.), potassium carbonate (25 g.), dimethyl sulphate (15 ml.), and dry acetone (100 ml.) were heated at 100° for 8 hr. Acetone was distilled off, and the residue treated with water and filtered. The precipitate was washed with alkali, then with water and with alcohol. Recrystallisation from acetic acid gave colourless needles of *tri-*O*-methylwedelolactone* (1·9 g.), m. p. 247° (Found : C, 63·7, 63·6; H, 4·8, 4·6; OMe, 33·5. $C_{19}H_{16}O_7$ requires C, 64·0; H, 4·5; 4OMe, 34·8%), recovered unchanged after refluxing with aniline or alcoholic ammonia.

*Tri-*O*-methylwedelic Acid*.—Tri-*O*-methylwedelolactone (1·5 g.) was refluxed with alcohol (100 ml.) containing potassium hydroxide (4 g.) for 4 hr. The solvent was removed *in vacuo*. The residue was dissolved in water, the solution filtered from amorphous material, and the filtrate made acidic. The precipitate was washed with water to give *tri-*O*-methylwedelic acid* (1·5 g.). Crystallisation from alcohol gave colourless needles which lost water at 192° and melted at 237—240° (Found : C, 61·4; H, 4·8. $C_{19}H_{18}O_8$ requires C, 61·0; H, 4·8%); in alcohol a deep orange colour was obtained with ferric chloride.

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[1] Horning and Horning, *J. Org. Chem.*, 1946, **11**, 95.

*Action of Heat on Tri-*O*-methylwedelic Acid.*—The acid (0·15 g.) was kept at 250—260° for 1 hr. The product was cooled, washed with alkali and then with water, and recrystallised from acetic acid to give needles, m. p. and mixed m. p. with tri-*O*-methylwedelolactone, 246—247°.

*Action of Methanolic Hydrogen Chloride on Tri-*O*-methylwedelic Acid.*—The acid (0·2 g.) in methanol (10 ml.) was saturated with dry hydrogen chloride at 0° and then refluxed for 5 hr. The precipitate was filtered off, and washed successively with alkali and water. Crystallisation from acetic acid gave colourless needles, m. p. and mixed m. p. with tri-*O*-methylwedelolactone, 245—246°.

*Methyl Tetra-*O*-methylwedelate.*—Tri-*O*-methylwedelic acid (0·9 g.) in ether (50 ml.) and methanol (25 ml.) was left with ethereal diazomethane (from 6 g. of methylnitrosourea) for 24 hr. The solvent was evaporated and the residue washed with sodium hydrogen carbonate solution and then with water. The dried material (0·86 g.) was digested with boiling methanol (50 ml.) and filtered. Concentration to 25 ml. and cooling gave *methyl tetra-*O*-methylwedelate* (0·55 g.), m. p. 166—167°, $\lambda_{max.}$ 310 mμ (log ε 4·21) (Found: C, 63·2; H, 5·8; OMe, 45·0. $C_{21}H_{22}O_8$ requires C, 62·7; H, 5·5; 6OMe, 46·3%), showing no colour with ferric chloride. The ester was unaffected by 2 : 4-dinitrophenylhydrazine, acetic anhydride in pyridine, potassium permanganate in acetone, or hydrogen at 60 lb./sq. in. in the presence of Adams catalyst.

The methanol-insoluble material from this esterification, on crystallisation from acetic acid, gave tri-*O*-methylwedelolactone (0·11 g.), m. p. 247°.

*Tetra-*O*-methylwedelic Acid.*—Methyl tetra-*O*-methylwedelate (1·03 g.) was refluxed with potassium hydroxide (3·4 g.) in water (10 ml.) and alcohol (10 ml.) for 4 hr. Alcohol was distilled off, and the solution diluted with water and filtered. Acidification and crystallisation of the precipitate from alcoholic acetic acid gave *tetra-*O*-methylwedelic acid* (0·6 g.), m. p. 225—228° (gas evolution) (Found: C, 62·3; H, 5·6%; equiv., 382. $C_{20}H_{20}O_8$ requires C, 61·9; H, 5·2%; equiv., 388).

A suspension of the acid (0·1 g.) in methanol (25 ml.) and ether (50 ml.) was left with ethereal diazomethane (from 2·5 g. of methylnitrosourea) for 24 hr. and then the solvent was evaporated. The residue was washed with alkali and then with water to give the ester (0·1 g.), m. p. and mixed m. p. with methyl tetra-*O*-methylwedelate, 165—167°.

*Decarboxylation of Tetra-*O*-methylwedelic Acid.*—The acid (0·5 g.) was heated at 240—260° for 2 hr. and the product sublimed at 150—160°/0·01 mm. The sublimate was ground with alkali, filtered, and washed with water, to give 5 : 6-*dimethoxy*-2-(2 : 4 : 6-*trimethoxyphenyl*)-*benzofuran* (0·4 g.), m. p. 143—145°. Recrystallisation from ether gave colourless needles (0·35 g.), m. p. 145°, $\lambda_{max.}$ 275 (log ε 4·15) and 310 mμ (log ε 4·35) (Found: C, 66·5, 66·6, 66·7; H, 5·8, 5·6, 6·0. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·8%), unaffected by acetic anhydride, hydroxylamine, potassium permanganate in acetone, or hydrogen as above.

Ozonolysis of 5 : 6-*Dimethoxy*-2-(2 : 4 : 6-*trimethoxyphenyl*)*benzofuran.*—A solution of the compound (1·2 g.) in chloroform (50 ml.) was treated with a 50% excess of ozone during 10 hr. at 0°. The solvent was then removed *in vacuo* at 30° and the ozonide refluxed for 1 hr. with water (110 ml.), zinc dust (0·35 g.), and a few crystals each of quinol and silver nitrate. The mixture was shaken with chloroform (50 ml.) and filtered. The filtrate was made acidic, the chloroform layer separated, and the aqueous layer extracted with more of the solvent. The combined extracts were washed successively with sodium hydrogen carbonate solution, dilute sodium hydroxide, and water, and then dried (Na_2SO_4). Evaporation and recrystallisation of the residue from methanol gave colourless needles of 6-(2 : 4 : 6-*trimethoxybenzoyloxy*)*veratraldehyde* (0·52 g.), m. p. 159—160°, $\lambda_{max.}$ 272 (log ε 4·27) and 318 mμ (log ε 3·94) (Found: 61·0, 61·1; H, 5·3, 5·3. $C_{19}H_{20}O_8$ requires C, 60·6; H, 5·3%), which afforded a 2 : 4-*dinitrophenylhydrazone*, orange needles (from acetic acid), 280—282° (decomp.) (Found: C, 53·8, 54·0; H, 4·3, 4·6; N, 10·0, 10·1. $C_{25}H_{24}O_{11}N_4$ requires C, 54·0; H, 4·3; N, 10·1%), *semicarbazone* (from dilute acetic acid), m. p. 213—215° (decomp.) (Found: C, 56·0; H, 5·7; N, 9·7. $C_{20}H_{23}O_8N_3$ requires C, 55·4; H, 5·3; N, 9·7%), and *dimedone derivative*, cubes (from dilute methanol), m. p. 171° (Found: C, 65·4; H, 6·8. $C_{35}H_{42}O_{11}$ requires C, 65·8; H, 6·6%).

The bicarbonate and alkaline extracts yielded, on acidification, small amounts of an acid and a phenol respectively, which were not characterised.

Hydrolysis of 6-(2 : 4 : 6-*Trimethoxybenzoyloxy*)*veratraldehyde.*—The ester (0·52 g.) was left with potassium hydroxide (2·7 g.), dissolved in alcohol (25 ml.), at 30° for 3 hr. with frequent shaking. The solvent was then removed at 30° *in vacuo* and water added to the residue. The clear yellow solution was saturated with carbon dioxide and extracted repeatedly with ether. The dried ether layer on evaporation gave 6-hydroxyveratraldehyde (0·25 g.), crystallising from light petroleum (b. p. 40—60°) as pale yellow needles, m. p. 105° alone or mixed with a synthetic specimen [2] (Found: C, 59·8, 59·5; H, 5·4, 5·1. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·5%), giving a dark green colour with ferric chloride, changing to brown on dilution, a *phenylhydrazone*, pale yellow plates (from light petroleum), m. p. 139—140° (Found: C, 66·3; H, 5·4. $C_{15}H_{16}O_3N_2$ requires C, 66·2; H, 5·9%), dimedone derivative (from dilute methanol), colourless plates, m. p. and mixed m. p. 191—193° (Found: C, 70·0, 70·1; H, 6·6, 6·8. Calc. for $C_9H_{10}O_4 + C_{16}H_{24}O_4 - 2H_2O$, *i.e.*, $C_{25}H_{30}O_6$: C, 70·4; H, 7·0%), methyl ether,[3] needles (from water), m. p. 113—114° after drying at 80°/5 mm., and benzoate (from light petroelum), colourless needles passing into pale yellow cubes, m. p. 100°.

The bicarbonate extract from the hydrolysis was acidified and extracted thoroughly with ether. Evaporation of the ether yielded a solid (0·21 g.), crystallising from benzene in colourless needles, m. p. 143° (decomp.) alone or mixed with synthetic 2 : 4 : 6-trimethoxybenzoic acid [4] (Found: C, 56·8, 56·5; H, 5·9, 5·7. Calc. for $C_{10}H_{12}O_5$: C, 56·6; H, 5·7%).

Attempted Demethylation of Wedelolactone.—The lactone (0·25 g.) and 48% hydrobromic acid (10 ml.) were refluxed for 1 hr., then diluted with water and filtered. Crystallisation from dilute alcohol yielded only *wedelic acid*, m. p. 333° (decomp.) (Found: C, 57·9; H, 3·7; OMe, 10·0. $C_{16}H_{12}O_8$ requires C, 57·8; H, 3·6; 1OMe, 9·3%).

Action of Hydrogen Peroxide on Wedelolactone.—The lactone (0·5 g.), dissolved in 5% potassium hydroxide solution (35 ml.), was left with hydrogen peroxide (100 ml.; 25-vol.) at 30° for 24 hr. The initially red solution soon became colourless. It was then heated at 60° for 2 hr., acidified, and extracted repeatedly with ether. The contents of the ether layer were separated into neutral (0·1 g.), phenolic (0·06 g.), and acidic (0·19 g.) fractions. The acidic part was sublimed *in vacuo* and the sublimate converted into the *p*-bromophenacyl ester, needles (from ethyl acetate), m. p. 209—211°, in too small a quantity for analysis. The neutral and the phenolic portion also could not be characterised.

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PRESIDENCY COLLEGE, MADRAS. [*Received, September 27th*, 1955.]

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[2] Arnold and Bordwell, *J. Amer. Chem. Soc.*, 1942, **64**, 2984.
[3] Head and Robertson, *J.*, 1930, 2434.
[4] Holmes, White, and Wilson, *J.*, 1950, 2810.