109. *Chemical Examination of* Wedelia calendulacea. *Part III.* Synthesis of Tri-O-methylwedelolactone.*

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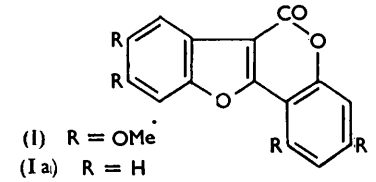
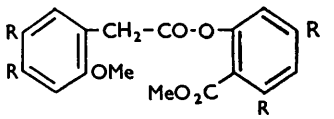
Syntheses of the parent ring system (Ia) and of tri-*O*-methylwedelolactone (I) are reported.

Syntheses of the parent ring system (Ia) present in wedelolactone and of tri-*O*-methylwedelolactone [1] (I) are reported here. Intramolecular Claisen condensation [2] of methyl *o*-*o*'-methoxyphenylacetoxybenzoate (II) gave the coumarin (III); demethylation of this with pyridine hydrochloride for a short time gave 4-hydroxy-3-*o*-hydroxyphenylcoumarin (IIIa) and the lactone (Ia) formed by simultaneous dehydration of (IIIa). The lactone also resulted by prolonged treatment of the coumarin (III) with pyridine hydrochloride or by heating of the coumarin (IIIa) at 280°.

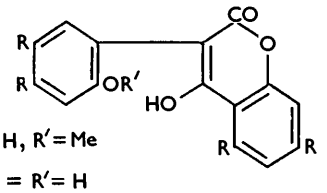
For a similar synthesis of tri-*O*-methylwedelolactone, methyl 2 : 4-dimethoxy-6-(2 : 4 : 5-trimethoxyphenylacetoxy)benzoate (IIa) could not be made by the action of 2 : 4 : 5-trimethoxyphenylacetyl chloride on methyl 6-hydroxy-2 : 4-dimethoxybenzoate.



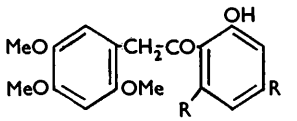
(I) R = OMe
(Ia) R = H



(II) R = H
(IIa) R = OMe



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



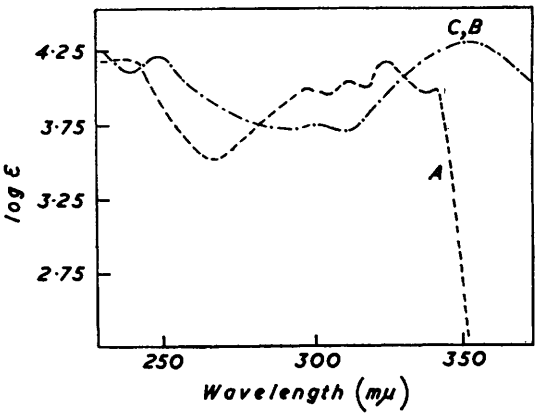
(IV) R = OH
(IVa) R = OMe

Attempts to prepare 2 : 4 : 6-trihydroxyphenyl 2 : 4 : 5-trimethoxybenzyl ketone (IV) which might have been converted through its dimethyl ether (IVa) and the coumarin (IIIb) into tri-*O*-methylwedelolactone (I) also failed since phloroglucinol could not be condensed with 2 : 4 : 5-trimethoxyphenylacetyl chloride in presence of aluminium chloride [3] or stannic chloride [4] or by heating it with the acid in presence of zinc chloride.[5] Finally, tri-*O*-methylwedelolactone was synthesised as follows : Asarylaldehyde, obtained in nearly quantitative yield from 1 : 2 : 4-trimethoxybenzene by treatment with dimethylformamide, was converted into 2 : 4 : 5-trimethoxybenzyl cyanide, through 2 : 4 : 5-trimethoxyphenylpyruvic acid. The deoxybenzoin (IV) obtained by a Hoesch reaction of this cyanide with phloroglucinol was converted by selective methylation [6] into the dimethyl ether (IVa) and thence by ethyl carbonate and sodium [6] into the coumarin (IIIb) which on fusion with pyridine hydrochloride followed by methylation yielded tri-*O*-methylwedelolactone (I) identical with that obtained from wedelolactone (mixed m. p. and ultraviolet spectrum, see Figure).

* Part II, preceding paper.

[1] Govindachari, Nagarajan, and Pai, *J.*, 1956, 629.
[2] Stahmann, Wolff, and Link, *J. Amer. Chem. Soc.*, 1943, **65**, 2285.
[3] Finzi, *Monatsh.*, 1905, **26**, 1125.
[4] Nam, Buu-Hoï, and Xuong, *J.*, 1954, 1690.
[5] Takei, Miyajima, and Ono, *Ber.*, 1932, **65**, 1047.
[6] Boyd, Robertson, and Whalley, *J.*, 1948, 174.

Before the completion of this work, we were informed by Dr. W. B. Whalley that compounds corresponding to tri-*O*-methylwedelolactone and its degradation product, 5 : 6-dimethoxy-2-(2 : 4 : 6-trimethoxyphenyl)benzofuran, had been synthesised by him and comparison with samples obtained from wedelolactone confirmed their identity.



Absorption spectra of (*A*) *lactone* (Ia) *and* (*B*) *synthetic and* (*C*) *natural tri*-O-*methylwedelolactone.*

Experimental

Ultraviolet measurements are for 95% ethanol solutions.

Methyl o-o'-*Methoxyphenylacetoxybenzoate.*—Methyl salicylate (8·5 g.) was refluxed with *o*-methoxyphenylacetyl chloride (from 10 g. of acid) in dry benzene (10 ml.) containing magnesium turnings (1 g.) on a water-bath for 6 hr. The mixture was filtered and the residue washed with ether. The combined filtrates were washed with 5% sodium hydroxide solution, then with water, and dried (Na_2SO_4). Evaporation of the solvent and crystallisation of the residue from dilute alcohol (charcoal) gave the *ester* (15 g.) as flakes and needles, m. p. 80° (Found : C, 68·2, 68·4; H, 5·6, 5·4. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%). This was obtained in poorer yields by refluxing the acid chloride and methyl salicylate till evolution of hydrogen chloride ceased or by heating them in the presence of dry pyridine. In both the cases, the product was purified by distillation. The fraction, b. p. 184—186°/0·8 mm., had m. p. 80°.

4-*Hydroxy*-3-o-*methoxyphenylcoumarin.*—The foregoing ester (6·4 g.) was added in small quantities to a vigorously stirred suspension of sodium (0·5 g.) in liquid paraffin (50 ml.; dried over sodium wire) at 240—250°, then heating and stirring were continued for 1 hr. The mixture was then cooled and the paraffin layer decanted. The residue was washed with light petroleum and dissolved in water (100 ml.), extracted with light petroleum, and made faintly acidic by hydrochloric acid. A scum separated and was removed by ether-extraction. The aqueous layer was made strongly acid (pH 1·5) and the sticky precipitate taken up in ether. The ether layer was dried (Na_2SO_4) and evaporated. The residue was washed with light petroleum and rubbed with ether, yielding a solid which, recrystallised from dilute alcohol, gave the *coumarin* (1·3 g.) as colourless needles, m. p. 176°, giving no colour with ferric chloride and dissolving in saturated sodium hydrogen carbonate solution. The *acetate*, prepared by acetic anhydride and a drop of pyridine at 100°, formed needles (from acetic acid), m. p. 204—205° (Found : C, 69·4, 69·3; H, 4·5, 4·6; OMe, 10·4. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·5; 1OMe, 10·0%). The use of excess of sodium at 280° in this reaction yielded a compound, m. p. 253°, identical with the coumarin described below.

4-*Hydroxy*-3-o-*hydroxyphenylcoumarin.*—The coumarin (1 g.) and pyridine hydrochloride (5 g.) were heated in a current of nitrogen at 220° for 6 min. The mixture was cooled immediately, treated with water (10 ml.), filtered, and washed with dilute alkali. Acidification of the filtrate with hydrochloric acid gave a substance (0·6 g.), which on recrystallisation from dilute alcohol yielded 4-*hydroxy*-3-o-*hydroxyphenylcoumarin* as needles, m. p. 253°, $\lambda_{infl.}$ 263 (log ε 3·94), $\lambda_{max.}$ 320 mμ (log ε 4·10) (Found : C, 71·3; H, 4·1; OMe, 0. $C_{15}H_{10}O_4$ requires C, 70·9; H, 3·9%), giving a dark green ferric colour. The alkali-insoluble residue (0·2 g.) from the demethylation was identical with the lactone described on p. 550.

Lactone of 2-o-Hydroxyphenylbenzofuran-3-carboxylic Acid.—(*a*) 4-Hydroxy-3-*o*-methoxyphenylcoumarin (0·2 g.) was fused with pyridine hydrochloride (2 g.) at 220° for 40 min. The product was treated with water, filtered off, and washed with alkali. After sublimation at 135—140°/1 mm., and crystallisation from methanol, the *lactone* was obtained as cream-coloured flakes, m. p. 181—182°, $\lambda_{max.}$ 233, 295, 310, 323 mμ (log ε 4·20, 4·02, 4·1, 4·2) (Found: C, 76·1; H, 3·1. $C_{15}H_8O_3$ requires C, 76·3; H, 3·4%).

(*b*) 4-Hydroxy-3-*o*-hydroxyphenylcoumarin (0·2 g.) was heated at 280° for 2 hr. The product was sublimed and the sublimate washed with alkali and recrystallised from methanol, to give the lactone, m. p. 181—182°.

1 : 2 : 4-*Triacetoxybenzene.*—Vliet's procedure [7] was successful only if the reaction time was short. Powdered quinone (10 g.) was added during 15 min. to stirred acetic anhydride (30 g.) containing sulphuric acid (2 g.) at 40—50°. The clear solution was poured into crushed ice, and the precipitate recrystallised from 95% alcohol to yield the triacetate (20—22 g.), m. p. 97°.

1 : 2 : 4-*Trimethoxybenzene.*—The directions of Bargellini and Martegiani [8] for obtaining this from 1 : 2 : 4-triacetoxybenzene were found to be inadequate. The triacetate (30 g.), dissolved in methanol (60 ml.) and methyl sulphate (105 ml.), was treated slowly with sodium hydroxide (90 g.) in water (90 ml.), with stirring. The mixture was cooled to 25—30°. After 1 hr. water (300 ml.) was added and the oil extracted with ether. Evaporation of the dried ether layer and distillation gave 1 : 2 : 4-trimethoxybenzene (15 g.), b. p. 247°/760 mm.

Asarylaldehyde.—1 : 2 : 4-Trimethoxybenzene (15 g.), *NN*-dimethylformamide (10 g.), and phosphorus oxychloride (9 ml.) were heated at 100° for 4½ hr. A saturated aqueous solution of sodium acetate (30 g.) was then added and the mixture refluxed for 30 min. On cooling, colourless needles separated and were filtered off and washed with water. Asarylaldehyde (14·6 g.), m. p. and mixed m. p. with a synthetic specimen,[9] 115°, was thus obtained.

2 : 4 : 5-*Trimethoxyphenylpyruvic Acid.*—Asarylaldehyde was treated with hippuric acid according to the directions of Takei, Miyajima, and Ono.[5] The azlactone (3·5 g.) was refluxed with sodium hydroxide (5·6 g.) in water (35 ml.) till evolution of ammonia ceased. The solution was cooled, saturated with sulphur dioxide, and filtered. The filtrate was treated at its b. p. with concentrated hydrochloric acid till no more sulphur dioxide was evolved. On cooling, the *pyruvic acid* (1·8 g.) separated and was obtained by crystallisation from alcohol as colourless cubes and needles, m. p. 192—194° (decomp.) (Found: C, 56·8; H, 5·5. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·5%).

The pyruvic acid (6 g.) and hydroxylamine hydrochloride (4 g.) in 10% sodium hydroxide solution (50 ml.) were warmed at 50—55°. After 24 hr. the solution was acidified with hydrochloric acid, and the precipitate collected and washed with ice-water. On recrystallisation from hot water, the *oxime* (6 g.) was obtained as colourless plates, m. p. 128—130° (decomp.). An analytical sample was dried for several days at 30°/0·5 mm. (Found: C, 53·1; H, 6·0. $C_{12}H_{15}O_6N$ requires C, 53·5; H, 5·6%).

2 : 4 : 5-*Trimethoxybenzyl Cyanide.*—The foregoing oxime (7 g.) was warmed cautiously with acetic anhydride (5 ml.) on the water-bath. After the vigorous reaction had subsided, water (50 ml.) was added, and the mixture cooled at 0°. After 12 hr. the precipitate was collected and washed with sodium hydrogen carbonate solution and then with water. Recrystallisation from 50% alcohol afforded 2 : 4 : 5-*trimethoxybenzyl cyanide* (4·2 g.), needles, m. p. 88·5° (Found: C, 64·2; H, 6·5. $C_{11}H_{13}O_3N$ requires C, 63·8; H, 6·3%).

2 : 4 : 6-*Trihydroxyphenyl* 2 : 4 : 5-*Trimethoxybenzyl Ketone.*—A slow stream of dry hydrogen chloride was passed for 5 hr. into a stirred, ice-cooled solution of anhydrous phloroglucinol (1·4 g.) and 2 : 4 : 5-trimethoxybenzyl cyanide (2 g.) in dry ether (40 ml.) containing anhydrous zinc chloride (0·8 g.). After 1 hr., the solid ketimine hydrochloride started to separate. The mixture was left at 0° for 24 hr. The hydrochloride was collected, washed with dry ether, dissolved in water (50 ml.), and refluxed for 2 hr. Crystallisation of the precipitate obtained on cooling, from aqueous alcohol, gave needles and plates of the *ketone* (1·5 g.), m. p. 208—209°. The analytical sample was dried at 140°/2 mm. (Found: C, 61·4; H, 5·7. $C_{17}H_{18}O_7$ requires C, 61·1; H, 5·4%). The ketone gave a reddish-brown ferric colour, and a blood-red colour with concentrated nitric acid.

2-*Hydroxy*-4 : 6-*dimethoxyphenyl* 2 : 4 : 5-*Trimethoxybenzyl Ketone.*—The foregoing ketone

[7] Vliet, *Org. Synth.*, Col. Vol. I, 1946, p. 317.
[8] Bargellini and Martegiani, *Gazzetta*, 1911, **41**, II, 448.
[9] Rajagopalan, Seshadri, and Varadarajan, *Proc. Indian Acad. Sci.*, 1949, **30**, 265.

(1 g.), methyl sulphate (0·8 g.), potassium carbonate (3 g.), and acetone (25 ml.) were heated on the water-bath for 14 hr. The *product* crystallised from alcohol as needles (0·8 g.), m. p. 144—145° (Found: C, 63·2; H, 6·6. $C_{19}H_{22}O_7$ requires C, 63·0; H, 6·1%), dissolving in 2N-sodium hydroxide with difficulty in the cold, but more readily on heating to give a yellow solution. It gave a blue colour with a drop of concentrated nitric acid, becoming red on dilution with water. With concentrated sulphuric acid, a pale green colour, deepening on warming and becoming red on dilution, was obtained.

4-Hydroxy-5 : 7-dimethoxy-3-(2 : 4 : 5-trimethoxyphenyl)coumarin.—The foregoing ketone (0·2 g.) in ethyl carbonate (5 ml.; distilled over phosphoric oxide) containing pulverised sodium (0·3 g.) was warmed on the water-bath for 20 min. The granular sodium salt which separated was treated with a small volume of methanol to decompose excess of sodium. Water (5 ml.) was added, and the solution, after repeated extraction with ether, made acidic to Congo-red. The gelatinous precipitate was washed, dried, and crystallised from alcohol and then from aqueous acetic acid, to yield the *coumarin* (0·13 g.), m. p. 272°, $\lambda_{max.}$ 313 mμ (log ε 4·07) (Found: C, 62·1; H, 5·6. $C_{20}H_{20}O_8$ requires C, 61·9; H, 5·2%), dissolving with difficulty in cold sodium hydrogen carbonate solution but readily on warming and having a negative ferric reaction. The *acetate*, prepared as above, had m. p. 240° (from acetic acid) (Found: C, 61·3; H, 5·2. $C_{22}H_{22}O_9$ requires C, 61·4; H, 5·1%). The *methyl ether*, prepared quantitatively by refluxing the coumarin (0·1 g.) with methyl iodide (1 ml.) and potassium carbonate (1 g.) in acetone (5 ml.), was obtained from aqueous alcohol as colourless needles, m. p. 185° (Found: C, 62·2; H, 5·8. $C_{21}H_{22}O_8$ requires C, 62·7; H, 5·5%).

Tri-O-methylwedelolactone.—The foregoing hydroxycoumarin (0·2 g.) was heated with dry pyridine hydrochloride (3 g.) at 240—250° in a current of nitrogen for 40 min., cooled, and treated with water (10 ml.). A light brown solid separated and was extracted repeatedly with ether. The dried (Na_2SO_4) ether layer was evaporated and the residue refluxed with methyl iodide (2 ml.) and potassium carbonate (1 g.) in dry acetone (5 ml.) for 8 hr. After removal of acetone, water was added and the mixture filtered. The residue was washed with alcohol and then recrystallised from acetic acid–alcohol mixture, to yield needles of *tri-O-methylwedelolactone* (20 mg.), m. p. and mixed m. p. 247—248°, $\lambda_{max.}$ 247, 300, 350 mμ (log ε 4·27, 3·80, 4·35) (Found: C, 64·0; H, 4·3. $C_{19}H_{16}O_7$ requires C, 64·0; H, 4·5%).

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