Fulgoicin, A New Depsidone from the Lichen *Fulgensia fulgida* (Nyl.)Szat.

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The synthesis of the depsidone 2,4-dichloro-3-hydroxy-8-methoxy-1,6,9-trimethyl-11*H*-dibenzo-[*b*,*e*][1,4]dioxepin-11-one (fulgoicin) is described.

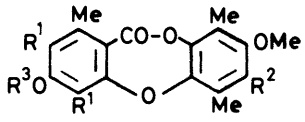
During a taxonomic study of the genus *Fulgensia*, two previously unreported depsidones—fulgoicin and fulgidin—together with the anthraquinone fragilin were isolated [1] from the lichen *Fulgensia fulgida* (Nyl.)Szat. Owing to constraints relating to the availability of the lichen material, structural elucidation of these two depsidones was limited to the use of spectroscopic methods. We now report a total synthesis of the dichlorodepsidone fulgoicin and confirm the assigned structure (1).

Our earlier success in synthesising the depsidone scensidin,[2] a constituent of the lichen *Buellia conescens*, encouraged us to use a similar reaction sequence for the synthesis of fulgoicin. The trihydroxybenzophenone (5) was selected as the target intermediate for the reasons reported earlier by Hendrickson *et al.*[3] that benzophenones bearing one or more halogeno substituents in one of the aromatic rings, give, upon oxidation, grisadienones, the hydroxy group of the halogenated ring of the benzophenone being oxidised. The resulting grisadienone (6) could then be converted into the depsidone fulgoicin by conventional methods.[2]

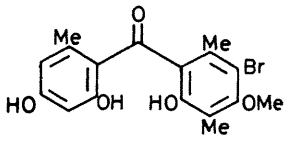
Methyl 2,4-dihydroxy-3,6-dimethylbenzoate (7) was brominated and the bromo ester (8) was methylated giving a mixture of the required ester (9) and its *O*-methyl derivative (10). However, the ester (9) was the sole product when methyl rhizinonate (11) was brominated. Benzylation of the ester (9), followed by hydrolysis of the bromoester (12) gave the acid (13).

Condensation of the acid (13) with *O*,*O*′-dibenzylorcinol (14) in boiling trifluoroacetic anhydride gave a multicomponent mixture (^{1}H n.m.r.) which, without purification, was hydrogenated giving the required trihydroxybenzophenone (5) in 67% yield.

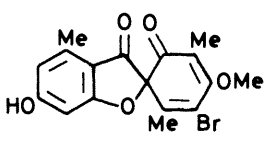
Oxidation of the trihydroxybenzophenone (5) with potassium hexaferrate(III) in aqueous potassium carbonate for 18 h gave only the depsidone (2). This reaction undoubtedly involves the intermediate grisadienone (6). A number of attempts to chlorinate the depsidone (2) or its acetyl derivative (3) using chlorine in carbon tetrachloride, chlorine in glacial acetic acid or *N*-chlorosuccinimide failed, although these reagents have been successfully used during the synthesis of the dipsidones diploicin [3,4] and vicanicin.[5] Ultimately, the depsidone (2) was chlorinated with chlorine in a mixture of acetic anhydride and acetic acid or chlorine in dichloromethane in the presence of a Lewis acid giving the dichlorodepsidone (4). Selective debromination of the depsidone (4) gave fulgoicin (1), identical in all respects with the natural product.



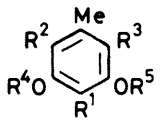
(1) R^1 = Cl; R^2 = R^3 = H (Fulgoicin)
(2) R^1 = R^3 = H; R^2 = Br
(3) R^1 = H; R^2 = Br; R^3 = Ac
(4) R^1 = Cl; R^2 = Br; R^3 = H



(5)



(6)



(7) R^1 = Me; R^2 = R^4 = R^5 = H; R^3 = CO_2Me
(8) R^1 = Me; R^2 = Br; R^3 = CO_2Me; R^4 = R^5 = H
(9) R^1 = R^4 = Me; R^2 = Br; R^3 = CO_2Me; R^5 = H
(10) R^1 = R^4 = R^5 = Me; R^2 = Br; R^3 = CO_2Me
(11) R^1 = R^4 = Me; R^2 = H; R^3 = CO_2Me; R^5 = H
(12) R^1 = R^4 = Me; R^2 = Br; R^3 = CO_2Me; R^5 = CH_2Ph
(13) R^1 = R^4 = Me; R^2 = Br; R^3 = CO_2H; R^5 = CH_2Ph
(14) R^1 = R^2 = R^3 = H; R^4 = R^5 = CH_2Ph

Experimental

General procedures used were those reported earlier.[2]

Methyl 5-Bromo-2,4-dihydroxy-3,6-dimethylbenzoate (8).—A solution of bromine (3.0 g, 18.8 mmol) in acetic acid (3 ml) was added dropwise to a stirred solution of the ester (7) [6] (4.8 g, 24.5 mmol) in carbon tetrachloride (50 ml) at room temperature. The mixture was further stirred for 1 h and then evaporated to dryness. The resulting solid was crystallised from a mixture of ether and n-hexane, giving the *benzoate* (8)

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as colourless crystals (6.5 g, 96%), m.p. 144—146 °C (Found: C, 43.4; H, 4.2; Br, 28.8%; $M^{+\cdot}$, 273.9846. $C_{10}H_{11}BrO_4$ requires C, 43.6; H, 4.0; Br, 29.1%; *M*, 273.9841), $\nu_{max.}$ ($CHCl_3$) 1 660 cm^{-1}; δ($CDCl_3$) 2.17 and 2.60 (6 H, 2 × s, 2 × ArMe), 3.94 (3 H, s, CO_2Me), 6.17 and 11.62 (2 H, 2 × s, 2 × ArOH).

Methyl 2-Hydroxy-4-methoxy-3,6-dimethylbenzoate (*Methyl Rhizinonate*) (11).—A solution of the ester (7)[6] (12.0 g, 61.2 mmol) in acetone (100 ml) was treated with an excess of an ethereal solution of diazomethane. After 18 h at room temperature, the excess of diazomethane was destroyed with acetic acid and the solution evaporated to dryness. Crystallisation of the residue from methanol gave the benzoate (11) as colourless crystals (12.3 g, 95%), m.p. 94—95 °C (lit.,[7] 101—102.5 °C), $\nu_{max.}$ ($CHCl_3$) 1 650 cm^{-1}; δ($CDCl_3$) 2.05 and 2.49 (6 H, 2 × s, 2 × ArMe), 3.81 (3 H, s, OMe), 3.89 (3 H, s, CO_2Me), 6.23 (1 H, s, ArH), and 11.79 (1 H, s, ArOH).

Methyl 5-Bromo-2-hydroxy-4-methoxy-3,6-dimethylbenzoate (9) *and Methyl 5-Bromo-2,4-dimethoxy-3,6-dimethylbenzoate* (10).—A solution of the bromo ester (8) (5.0 g, 18.2 mmol) in acetone (50 ml) was treated with an excess of an ethereal solution of diazomethane. After 10 min at room temperature the solution was worked up as described for the ester (11). The residual solid was fractionated by preparative t.l.c. on silica gel using chloroform as eluant. Two major bands were separated.

The product constituting the slower moving band, after crystallisation from methanol, gave the *benzoate* (9) as colourless crystals (3.2 g, 60%), m.p. 64—65 °C (Found: C, 45.4; H, 4.2; Br, 28.0%; $M^{+\cdot}$, 287.9998. $C_{11}H_{13}BrO_4$ requires C, 45.7; H, 4.5; Br, 27.7%; *M*, 287.9998); $\nu_{max.}$ ($CHCl_3$) 1 670 cm^{-1}; δ($CDCl_3$) 2.19 and 2.60 (6 H, 2 × s, 2 × ArMe), 3.77 (3 H, s, OMe), 3.94 (3 H, s, CO_2Me), and 11.33br (1 H, s, ArOH).

The ester (9) was also prepared in 97% yield from methyl rhizinonate (11) (35.7 mmol) and bromine (35.8 mmol) in carbon tetrachloride (100 ml), the mixture being stirred at room temperature for 30 min and then worked up.

The product giving the faster moving band was crystallised from methanol and yielded methyl 5-bromo-2,4-methoxy-3,6-dimethylbenzoate (10) as colourless crystals (1.6 g, 27%), m.p. 73—74 °C (lit.,[7] 78—79 °C) (Found: $M^{+\cdot}$, 302.0154. Calc. for $C_{12}H_{15}BrO_4$: *M*, 302.0154), $\nu_{max.}$ ($CHCl_3$) 1 725 cm^{-1}; δ($CDCl_3$) 2.21 and 2.28 (6 H, 2 × s, 2 × ArMe), 3.71 and 3.74 (6 H, 2 × s, 2 × OMe), and 3.87 (3 H, s, CO_2Me).

Methyl 2-Benzyloxy-5-bromo-4-methoxy-3,6-dimethylbenzoate (12).—To a solution of the ester (9) (2.9 g, 10.1 mmol) in acetone (150 ml) was added fused potassium carbonate (4.0 g) and benzyl bromide (2.0 g). The stirred mixture was heated under reflux for 18 h, and then cooled, filtered, and the filtrate evaporated to dryness. The residue was fractionated on a silica gel column using light petroleum followed by acetone as eluants. This gave the *benzoate* (12) as a colourless oil (3.7 g, 97%) (Found: C, 57.1; H, 4.9; Br, 21.3%; $M^{+\cdot}$, 378.0461. $C_{18}H_{19}BrO_4$ requires C, 57.0; H, 5.0; Br, 21.1%; *M*, 378.0467), $\nu_{max.}$ ($CHCl_3$) 1 730 cm^{-1}; δ($CDCl_3$) 2.26 and 2.34 (6 H, 2 × s, 2 × ArMe), 3.78 (3 H, s, OMe), 3.81 (3 H s, CO_2Me), 4.89 (2 H, s, $ArCH_2$), and 7.28—7.45 (5 H, m, ArH).

2-Benzyloxy-5-bromo-4-methoxy-3,6-dimethylbenzoic Acid (13).—To a solution of the ester (12) (3.0 g, 7.9 mmol) in methanol (100 ml) was added 10M-aqueous potassium hydroxide (100 ml); the mixture was then heated under reflux for 24 h. Methanol was removed under reduced pressure and the residue was diluted with water, acidified, and extracted into ethyl acetate. The organic layer was then shaken with aqueous sodium hydrogen carbonate and the basic extract acidified. The resulting precipitate was collected, dried, and crystallised from ethyl acetate to give the *benzoic acid* (13) as colourless crystals (2.5 g, 86%), m.p. 155—156 °C (Found: C, 55.8; H, 4.9; Br, 21.8%; $M^{+\cdot}$, 364. $C_{17}H_{17}BrO_4$ requires C, 55.9; H, 4.7; Br, 21.9%, *M*, 364), $\nu_{max.}$ ($CHCl_3$) 1 710 cm^{-1}; δ($CDCl_3$) 2.28 (6 H, 2 × s, 2 × ArMe), 3.79 (3 H, s, OMe), 4.97 (2 H, s, $ArCH_2$), and 7.22—7.55 (5 H, m, ArH).

5'-Bromo-2,2',4-trihydroxy-4'-methoxy-3',6,6'-trimethylbenzophenone (5).—A stirred suspension of the acid (13) (0.91 g, 2.5 mmol) and *O,O'*-dibenzylorcinol (14)[3] (0.7 g, 2.3 mmol) in trifluoroacetic anhydride (50 ml) was heated under reflux for 1.5 h. The mixture was cooled and the supernatant liquid was decanted from an orange-green oil.

A solution of the above oil in ethyl acetate (50 ml) was stirred in the presence of palladium and charcoal (0.1 g, 10%) under an atmosphere of hydrogen until the uptake of hydrogen had ceased. The mixture was filtered, concentrated, and the residue fractionated by preparative t.l.c. on silica gel using chloroform–ethyl acetate (8 : 2) as the eluant. The *benzophenone* (5), after crystallisation from chloroform, gave yellow crystals (0.64 g, 67%), m.p. 177—178 °C (Found: C, 53.6; H, 4.7; Br, 21.2%; $M^{+\cdot}$, 380. $C_{17}H_{17}BrO_5$ requires C, 53.5; H, 4.5; Br, 21.0%, *M*, 380), $\nu_{max.}$ ($CHCl_3$) 1 615 cm^{-1}; δ($CDCl_3$) 1.75, 2.10, and 2.20 (9 H, 3 × s, 3 × ArMe), 3.79 (3 H, s, OMe), and 6.14 and 6.26 (2 H, 2 × s, 2 × ArH).

7-Bromo-3-hydroxy-8-methoxy-1,6,9-trimethyl-11H-dibenzo[b,e][1,4]dioxepin-11-one (2).—To a stirred solution of the benzophenone (5) (0.1 g, 0.3 mmol) and potassium carbonate (2.0 g) in water (20 ml) was added in one portion a solution of potassium hexacyanoferrate(III) (0.15 g) in water (20 ml). After 18 h at room temperature, the solution was cooled, acidified with dilute hydrochloric acid, and shaken with ethyl acetate. The organic layer was washed with water, dried, and evaporated to dryness. The residual solid was crystallised from methanol to give the *depsidone* (2) as colourless crystals (80 mg, 85%), m.p. 219 °C (decomp.) (Found: C, 53.8; H, 3.6; Br, 21.1%; $M^{+\cdot}$, 378. $C_{15}H_{17}BrO_5$ requires C, 53.8; H, 3.9; Br, 21.1%; *M*, 378); $\nu_{max.}$ (KBr) 1 685 cm^{-1}; δ(C_5D_5N) 2.26, 2.42, and 2.54 (9 H, 3 × s, 3 × ArMe), 3.64 (3 H, s, OMe), 6.85 (1 H, d, *J* 2.5 Hz, ArH), and 6.91 (1 H, d, *J* 2.5 Hz, ArH).

3-Acetoxy-7-bromo-8-methoxy-1,6,9-trimethyl-11H-dibenzo[b,e][1,4]dioxepin-11-one (3).—To a solution of the depsidone (2) (0.1 g, 0.4 mmol) in acetic acid (3 ml) was added concentrated sulphuric acid (4 drops). The mixture was stirred at room temperature for 18 h, and then poured into ice–water and shaken with ethyl acetate. The organic layer was washed with water, dried, and evaporated to dryness. The residue was crystallised from methanol to give the *depsidone* (3) as colourless crystals (0.1 g, 89%), m.p. 196—197 °C (Found: $M^{+\cdot}$, 420.0240. $C_{19}H_{17}BrO_6$ requires *M*, 420.0208), $\nu_{max.}$ ($CHCl_3$) 1 690 and 1 625 cm^{-1}; δ($CDCl_3$) 2.31 (3 H, s, ArMe) and 2.51 (3 H, s, OCOMe), 3.75 (3 H, s, OMe), 6.86 and 6.91 (2 H, 2 × s, 2 × ArH).

7-Bromo-2,4-dichloro-3-hydroxy-8-methoxy-1,6,9-trimethyl-11H-dibenzo[b,e][1,4]dioxepin-11-one (4).—(i) To a stirred solution of the depsidone (2) (0.1 g, 0.4 mmol) in a mixture of acetic acid (3 ml) and acetic anhydride (2 ml) was added an excess of chlorine in a mixture of acetic acid and acetic anhydride in the same ratio. The solution was stirred at room temperature in the dark for 0.5 h and then poured into water. A greenish yellow solid was collected, washed with water,

dried, and fractionated by t.l.c. using silica gel and chloroform–light petroleum mixture (b.p. 60—80 °C) (3 : 7) as the eluant. After development of the plates four times using the same solvent system, the major band was removed. Extraction of the silica gel gave a solid which crystallised from methanol and gave the *depsidone* (4) as colourless crystals (20 mg, 17%), m.p. 258—259 °C (Found: $M^{+\cdot}$, 445.9331. $C_{17}H_{13}BrCl_2O_5$ requires M, 445.9324), $\nu_{max.}$ (KBr) 1 710 cm^{-1}; $\delta(CDCl_3 + C_5D_5N)$ 2.30, 2.50, and 2.60 (total 9 H, 3 × s, 3 × ArMe), and 3.70 (3 H, s, OMe).

(ii) Anhydrous aluminium chloride (10 mg) was added to a stirred solution of the depsidone (2) (50 mg, 0.13 mmol) in dichloromethane (20 ml). The resulting greenish yellow solution was treated with an excess of chlorine in dichloromethane. The mixture was stirred at room temperature for 45 min, poured onto an ice–water slurry, and then shaken with ethyl acetate. After being washed with water, the organic layer was dried and evaporated to leave an oil which was purified as described in (i) giving the depsidone (4) (30 mg, 51%).

Fulgoicin (1).—A stirred solution of the depsidone (4) (50 mg, 0.1 mmol) and anhydrous sodium acetate (80 mg) in methanol (25 ml) was hydrogenated in the presence of palladium and charcoal (50 mg, 10%) at room temperature and atmospheric pressure of hydrogen. After the uptake of hydrogen had ceased, the mixture was filtered; the filtrate was poured into water and shaken with ethyl acetate. The washed and dried ethyl acetate extract was evaporated and the residual solid crystallised from methanol to give fulgoicin (1) as colourless crystals (22 mg, 54%), m.p. 222—223 °C (lit.,[1] 220 °C), identical with the natural product isolated from *Fulgensia fulgida* $\nu_{max.}$ ($CHCl_3$) 1 740 and 3 510 cm^{-1}; $\delta(CDCl_3)$ 2.20, 2.51, and 2.53 (total 9 H, 3 × s, 3 × ArMe), 3.79 (3 H, s, OMe) and 6.46 (1 H, s, ArH); $M^{+\cdot}$, 368,370, and 372 in the ratios 9 : 6 : 1 ($C_{17}H_{14}Cl_2O_5$).

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Received 17*th March* 1983; *Paper* 3/416