Depsidone Synthesis. Part 15.[1] New Metabolites of the Lichen *Buellia canescens* (Dicks.) De Not: Novel Phthalide Catabolites of Depsidones [2]

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The isolation, from the lichen *Buellia canescens* (Dicks.) De Not., and structural determination of the new depsidones 2,7,9-trichloro-3-hydroxy-8-methoxy-1,6-dimethyldibenzo[*b,e*][1,4]dioxepin-11-one (dechlorodiploicin) (1) and its methyl ether dechloro-*O*-methyldiploicin (9), together with the novel phthalides 4-chloro-7-(3,5-dichloro-4,6-dimethoxy-2-methylphenoxy)-5-methoxyisobenzofuran-1(3*H*)-one (buellolide) (13) and 4,6-dichloro-7-(2,4-dichloro-3,6-dimethoxy-5-methylphenoxy)-5-methoxyisobenzofuran-1(3*H*)-one (canesolide) (18) are described. The synthesis of buellolide (13) is also described. It is postulated that buellolide (13) and canesolide (18) arise by catabolism of their congeneric depsidones, in the latter case with Smiles rearrangement.

THE biosynthesis of depsidones is thought to involve the oxidative coupling of *p*-depsides,[3] although the evidence is circumstantial. This coupling has only been achieved *in vitro* in one case,[4] in spite of other efforts.[5] Although depside–depsidone pairs of exactly corresponding structures are known their occurrence is only rarely in the same lichen species.[6]

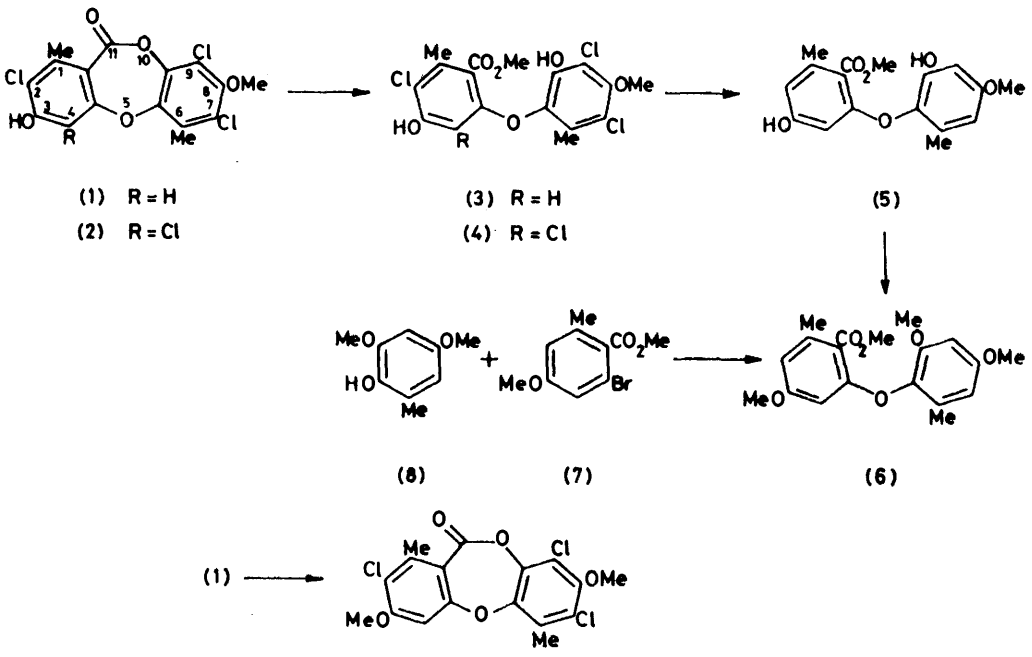
In a search for possible intermediates involved in the biosynthesis of depsidones we have subjected an extract of the lichen *Buellia canescens* to a detailed scrutiny. This lichen is known to produce diploicin (2) [7,8] the biosynthetically simplest of the known depsidones. Nolan and his co-workers [7] have also reported the isolation of another diploicin-like substance $C_{15}H_8Cl_3O_4$ (OMe), m.p. 257 °C, from this source but insufficient material was obtained for structural work. We have isolated from the lichen, collected on the coast of New South Wales, the known depsidone diploicin (2), the new depsidones dechloro-diploicin (1), m.p. 272.5—274 °C, and dechloro-*O*-methyldiploicin (9), and the unusual phthalides (13) and (18) for which we suggest the trivial names buellolide and canesolide. Dechlorodiploicin (1) is probably identical with the compound, m.p. 257 °C, isolated by Nolan and his co-workers.[7]

The presence in the i.r. spectrum of dechlorodiploicin (1) of a carbonyl stretching band at 1 756 cm^{-1} suggested that it was a depsidone. The close relationship of dechlorodiploicin (1) to diploicin (2) was demonstrated by the spectroscopic data. The mass spectrum of dechlorodiploicin (1) indicated the molecular formula $C_{16}H_{11}Cl_3O_5$ and the ^1H n.m.r. spectrum revealed the presence of an aromatic proton, two aromatic C–Me groups, and a methoxy-group. In order to establish the structure of dechlorodiploicin we sought to degrade both it and diploicin (2) to the same diaryl ether. Methanolysis of dechlorodiploicin (1) (Scheme 1) gave the diaryl ether (3), which was subjected to hydrogenolysis and furnished the dechloro-compound (5). Similarly diploicin (2) was converted *via* the diaryl ether (4) into a dechloro-compound which was identical to compound (5) obtained from dechlorodiploicin (1). Both compounds (3) and (5) exhibited high-field aromatic-proton signals in their ^1H n.m.r. spectra typical of tri-*ortho*-substituted diaryl ethers,[5] and this evidence was used to fix the position of the chloro-substituents in dechlorodiploicin (1). Given the structure of diploicin and assuming no rearrangement during the methanolysis of diploicin and dechlorodiploicin the above degradation is proof of structure (2) for dechlorodiploicin. However, depsidones with electron-withdrawing substituents at the 4- and 6-positions sometimes undergo methoxide-induced methanolysis with Smiles rearrangement.[9] The structure of diploicin (2) has been confirmed by an unambiguous synthesis which avoids reaction conditions conducive to possible Smiles rearrangement.[10] That no rearrangement had occurred during the methanolysis of diploicin (2), and by analogy in that of dechlorodiploicin (1), was demonstrated by the Ullmann synthesis from the bromo-compound (7) [11] and the phenol (8) [12] of the diaryl ether (6). This last compound was identical with that obtained by methylation of the degradation product (5). Dechlorodiploicin is thus represented by structure (1).

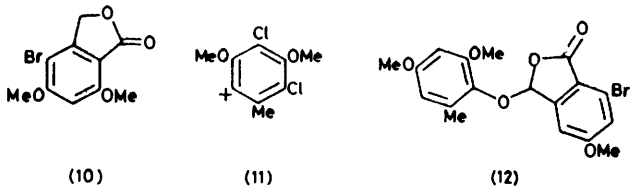
The other new depsidone, dechloro-*O*-methyldiploicin, must possess structure (9) since it was obtained by methylation of dechlorodiploicin (1).

The molecular formula, $C_{18}H_{15}Cl_3O_5$, of buellolide (13) was established by mass spectrometry, and the ^1H n.m.r. spectrum indicated the presence of an aromatic proton which resonated at high field, an aromatic C–Me group, three methoxy-groups, and a signal attributed to the methylene protons of a phthalide. The presence of the phthalide moiety was supported by a carbonyl-stretching band in the i.r. spectrum of buellolide at 1 781 cm^{-1}. The electronic spectrum of buellolide (13) was also very similar to that of the phthalide (10).[13] The base peak in the high-resolution mass spectrum of buellolide (13) was attributed to the ion (11). On hydrogenolysis, buellolide (13) gave the dechloro-compound (14) (Scheme 2) which, like buellolide exhibited a high-field aromatic-proton signal, suggestive

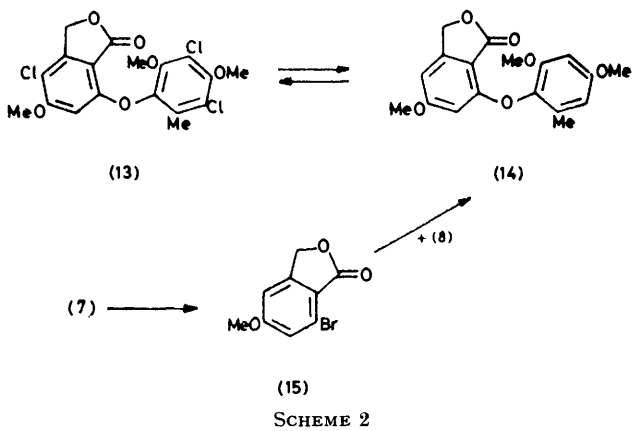
of a tri-*ortho*-substituted diaryl ether,[5] in its ^1H n.m.r. spectrum. Assuming a polyketide derivation these data may be rationalized by structure (13) for buellolide. This structure was supported by the synthesis of the dechloro-compound (14). Photobromination of the bromo-compound (7) [11] and subsequent steps readily gave the bromophthalide (15). Ullmann reaction of the latter with the phenol (8) [12] then gave the dechloro-compound (14), identical with that obtained by degradation of buellolide (13). A by-product isolated from this reaction was assigned the pseudo-ester structure (12) on the grounds of its spectroscopic data. On treatment with an excess of sulphuryl chloride in dichloromethane the dechloro-compound (14) gave synthetic buellolide (13), identical with the natural product.



SCHEME 1



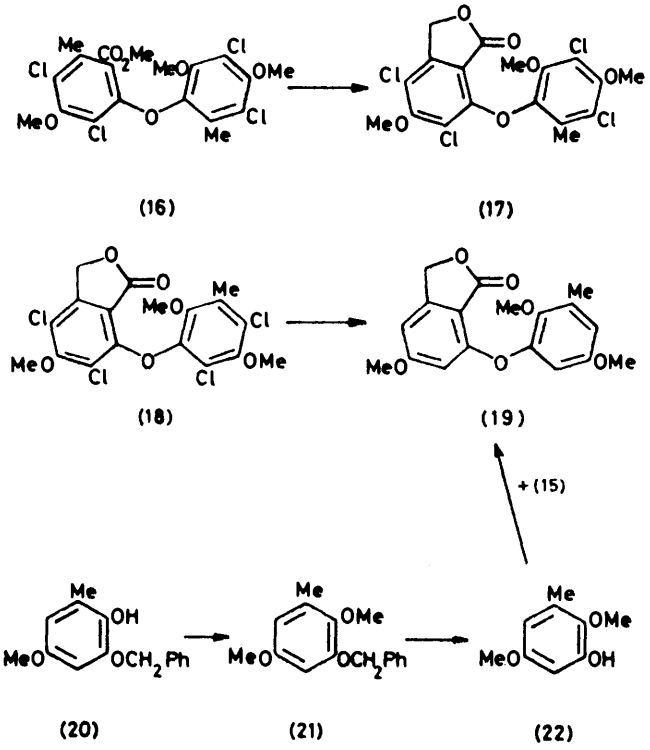
The spectroscopic properties of canesolide, $C_{18}H_{14}Cl_4O_5$, were very similar to those of buellolide (13), hence structure (17) (Scheme 3) appeared likely. Attempts to introduce a chlorine atom into the vacant sterically hindered nuclear position of buellolide (13) were fruitless. Hence the diploicin degradation product (16) was converted in low yield by photobromination and subsequent steps into compound (17). This product, unexpectedly, was different from canesolide. Speculation on the possible mode of biogenesis of canesolide (see later) led to the proposal of structure (18), and hence structure (19) for the hydrogenolysis product of canesolide. These structural proposals were verified by the synthesis of the hydrogenolysis product (19). The phenol (20), available from our total synthesis of diploicin,[10] was methylated and the product (21) was subjected to hydrogenolysis. The resultant phenol (22) on Ullmann reaction with the bromo-compound (15) then gave tetradechlorocanesolide (19), identical with that obtained by hydrogenolysis of the natural product.



SCHEME 2

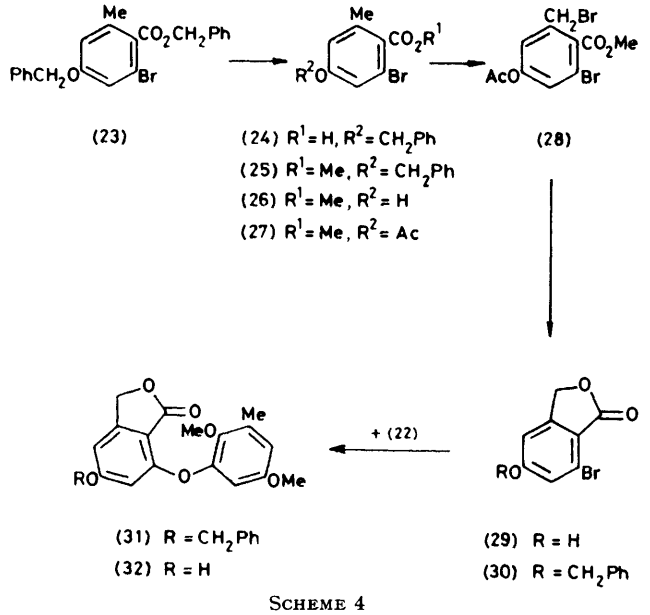
Attempts to obtain canesolide (18) by chlorination of compound (19) were not successful. The phenol (32), obtained by the rational sequence of steps outlined in

Scheme 4 and detailed in the Experimental section, was synthesized in the expectation that it would be more prone to undergo chlorination than compound (12). Norcanesolide was not obtained by attempted chlorination of the phenol (32) under a wide range of conditions.

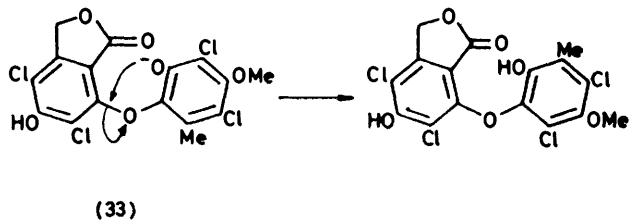


Scheme 3

Buellolide (13) and canesolide (18) probably arise biogenetically by catabolism of their congeric depsidones. Thus dechlorodiploicin (1) or dechloro-*O*-methyldiploicin (9) would undergo fission of the depside linkage, oxidation of the methyl group at the 1-position, and *O*-methylation, thus yielding buellolide (13). Canesolide (18), however, would arise from diploicin (2) by a similar sequence, but the fission of the depside linkage, in this case, must be accompanied by a Smiles rearrangement (Scheme 5). Although diploicin (2) does not undergo a

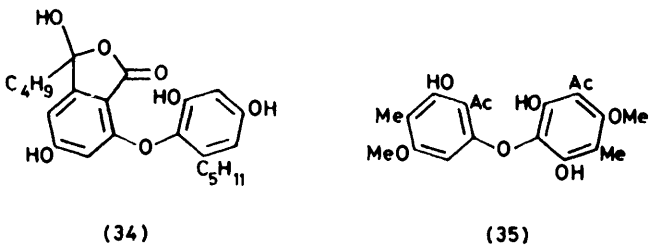


Scheme 4



Scheme 5

Smiles rearrangement on methanolysis *in vitro*, the rearrangement of the phenoxide ion (33) *in vivo* is not precluded. It is known that the Smiles rearrangement is highly sensitive to steric [14] and to solvent [9] effects. The



intervention of the Smiles rearrangement in the biosynthesis of the depsidones of *Chaetomium mollicellum* [15] is discussed in the following paper.

Diaryl ethers are rarely found in lichens; the only other examples are norlobaridol (34) [16] and leprolomin (35).[17] Norlobaridol (34) is a depsidone cleavage product but the biosynthesis of leprolomin (35) must follow a different course.[17]

EXPERIMENTAL

General directions have been published previously.[18] Electronic spectra were determined for ethanolic solutions with a Beckman Acta MIV spectrophotometer.

Extraction of Buellia canescens (*Dicks.*) *De Not.*—The lichen and adhering rocks were collected along the foreshore at Mystery Bay, New South Wales, and these were covered with dry acetone and allowed to stand for 48 h. The process was repeated twice more and the combined extracts were filtered and evaporated under reduced pressure. The crude gummy residue (*ca.* 2 g) was chromatographed over silica gel with light petroleum–benzene then ethyl acetate–benzene as eluants. Further purification was effected by rechromatography and, or preparative t.l.c. and crystallization. In order of decreasing R_F in 10% ethyl acetate–light petroleum the following were isolated: a mixture (189 mg) of atranorin and chloroatranorin [7] which was identified by comparison with authentic material; 2,7,9-*trichloro*-3,8-*dimethoxy*-1,6-*dimethyldibenzo*[b,e][1,4]*dioxepin*-11-*one* (*dechloro*-O-*methyldiploicin*) (9) (14.2 mg) which was purified by preparative t.l.c. (5% ethyl acetate–light petroleum) and formed needles (from dichloromethane–light

petroleum), m.p. 230—231.5 °C (Found: M^+, 401.982 8. $^{12}C_{17}{}^{1}H_{13}{}^{35}Cl_3{}^{16}O_5$ requires M, 401.982 8); δ($CDCl_3$, 60 MHz) 2.47 and 2.51 (each 3 H, s, Me), 3.81 and 3.92 (each 3 H, s, OMe), and 6.59 (1 H, s, ArH); $\nu_{max.}$ (CCl_4) 1 758 (C=O) and 1 598 (C=C) cm^{-1}; *m/e* 406 (14%), 404 (28), 402 (28, M^+), 370 (21), 369 (62), 368 (24), 367 (100), 354 (17), 352 (28), 341 (26), 339 (35), 325 (17), and 323 (19); diploicin (2) (246 mg) which formed needles (from ethanol), m.p. and mixed m.p. 231—232 °C (lit.,[7] 232 °C); *4-chloro-7-(3,5-dichloro-2-methyl-4,6-dimethoxy-2-methylphenoxy)-5-methoxyisobenzofuran-1(3H)-one* (*buellolide*) (13) (117.6 mg) which was purified by preparative t.l.c. (benzene) and formed prisms (from dichloromethane–light petroleum), m.p. 170—173 °C (Found: M^+, 431.989 1. $^{12}C_{18}{}^{1}H_{15}{}^{35}Cl_3{}^{16}O_6$ requires M, 431.993 4); δ($CDCl_3$, 90 MHz) 2.28 (3 H, s, Me), 3.76, 3.85, and 3.94 (each 3 H, s, OMe), 5.23 (2 H, s, CH_2), and 6.01 (1 H, s, ArH); irradiation at δ 5.23 sharpened the ArH signal, and irradiation at δ 6.01 sharpened the CH_2 signal; $\nu_{max.}$ (CCl_4) 1 781 (C=O) cm^{-1}; *m/e* 436 (12%), 435 (8), 434 (37), 433 (7), 432 (34, M^+), 223 (13), 222 (8), 221 (69), 220 (12), 219 (100, $C_9H_9{}^{35}Cl_2O_2$), 178 (11), 176 (10), and 169 (9); $\lambda_{max.}$ 224 (ε 44 100), 259 (15 500), and 295 nm (5 200), $\lambda_{infl.}$ 288 (ε 4 800) and 320 nm (600); *4,6-dichloro-7-(2,4-dichloro-3,6-dimethoxy-5-methylphenoxy)-5-methoxyisobenzofuran-1(3H)-one* (*canesolide*) (18) (44.3 mg) which was purified by preparative t.l.c. (benzene) and formed prisms (from dichloromethane–light petroleum), m.p. 158—160 °C (Found: M^+, 465.955 9. $^{12}C_{18}{}^{1}H_{14}{}^{35}Cl_4{}^{16}O_6$ requires M, 465.954 4); δ($CDCl_3$, 90 MHz) 2.25 (3 H, s, Me), 3.59, 3.89, and 4.01 (each 3 H, s, OMe), and 5.16 (2 H, s, CH_2); $\nu_{max.}$ (CCl_4) 1 788 (C=O) cm^{-1}; *m/e* 472 (13%), 471 (12), 470 (50), 469 (22), 468 (100), 467 (18), 466 (72, M^+), 455 (28), 454 (12), 453 (53), 452 (10), 451 (43), 433 (13), 431 (13), 221 (16), 219 (10), 205 (12), 178 (14), and 176 (21); *2,7,9-trichloro-3-hydroxy-8-methoxy-1,6-dimethyldibenzo*[b,e][1,4]*dioxepin-11-one* (*dechlorodiploicin*) (1) (30 mg) which was purified by preparative t.l.c. (5% ethyl acetate–light petroleum) and formed needles (from methanol), m.p. 272.5—274 °C (Found: M^+, 387.967 1. $^{12}C_{16}{}^{1}H_{11}{}^{35}Cl_3{}^{16}O_5$ requires M, 387.967 1); δ($CDCl_3$–CD_3SOCD_3, 90 MHz) 2.49 and 2.52 (each 3 H, s, Me), 3.85 (3 H, s, OMe), and 6.82 (1 H, s, ArH); $\nu_{max.}$ ($CHCl_3$) 1 756 (C=O) and 1 604 (C=C) cm^{-1}; *m/e* 392 (10), 390 (29), 388 (29, M^+), 357 (14), 356 (14), 355 (70), 353 (100), 340 (13), 338 (19), 327 (21), 326 (10), 325 (29), 311 (10), 309 (16), 297 (10), 233 (11), 143 (10), 142 (11), and 140 (10).

Degradation of Dechlorodiploicin (1).—The depsidone (1) (25 mg) and sodium methoxide [from sodium (20 mg)] were stirred in dry methanol (15 ml) for 2 h. The solution was poured into dilute hydrochloric acid and then extracted with ethyl acetate. The usual work-up gave *methyl 3-chloro-6-(3,5-dichloro-2-hydroxy-4-methoxy-6-methylphenoxy)-4-hydroxy-2-methylbenzoate* (3) (20 mg) as prisms (from dichloromethane–light petroleum), m.p. 175—176.5 °C (Found: M^+, 419.986 6. $^{12}C_{17}{}^{1}H_{15}{}^{35}Cl_3{}^{16}O_6$ requires M, 419.993 4); δ($CDCl_3$, 60 MHz) 2.26 and 2.40 (each 3 H, s, Me), 3.84 and 3.94 (each 3 H, s, OMe), and 6.11 (1 H, s, ArH). This material (19.0 mg), triethylamine (0.5 ml), and methanol (15 ml) were shaken with 10% palladium–charcoal (Engelhard) (100 mg) under 4 atm of hydrogen for 60 h. The usual work-up followed by preparative t.l.c. (15% v/v ethyl acetate–light petroleum) gave *methyl 4-hydroxy-6-(2-hydroxy-4-methoxy-6-methylphenoxy)-2-methylbenzoate* (5) (9.7 mg) as prisms (from dichloromethane–light petroleum), m.p. 136—137 °C (Found: M^+, 318.110 3. $^{12}C_{17}{}^{1}H_{18}{}^{16}O_6$ requires M, 318.110 3); δ($CDCl_3$, 90 MHz) 2.17 (3 H, s, $W_{\frac{1}{2}}$ 1.9 Hz, Me), 2.30 (3 H, s, $W_{\frac{1}{2}}$ 1.8 Hz, Me), 3.73 and 3.95 (each 3 H, s, OMe), 5.96 and 6.30 (2 H, br AB, J 2.5 Hz, ArH), 6.30 and 6.38 (2 H, br AB, J 2.5 Hz, ArH). Irradiation at δ 2.30 sharpened the higher field AB system, whilst irradiation at δ 2.17 sharpened the lower field AB system; *m/e*, 318 (53%, M^+), 153 (20, $C_8H_9O_3$), 151 (17, $C_8H_7O_3$), and 136 (100, $C_8H_8O_2$). On methylation in the usual way with iodomethane, and potassium carbonate in dry *NN*-dimethylformamide under dry nitrogen, compound (5) gave *methyl 6-(2,4-dimethoxy-6-methylphenoxy)-4-methoxy-2-methylbenzoate* (6) as needles (from methanol), m.p. 82—83 °C (Found: M,$^+$ 346.141 5. $^{12}C_{19}{}^{1}H_{22}{}^{16}O_6$ requires M, 346.141 6); δ($CDCl_3$, 90 MHz) 2.13 and 2.34 (each 3 H, s, $W_{\frac{1}{2}}$ 1.8 Hz, Me), 3.63, 3.71, 3.77, and 3.89 (each 3 H, s, OMe), 5.86 and 6.32 (2 H, br AB, J 2.5 Hz, ArH), 6.32 and 6.39 (2 H, br AB, J 2.5 Hz, ArH). Irradiation at δ 2.34 sharpened the higher field AB system, and irradiation at δ 2.13 sharpened the lower field AB system.

Degradation of Diploicin (2).—Methanolysis of diploicin (2) as before gave methyl 3,5-dichloro-6-(3,5-dichloro-2-hydroxy-4-methoxy-6-methylphenoxy)-4-hydroxy-2-methylbenzoate (4) (93%) as needles (from dichloromethane–light petroleum), m.p. 199—200 °C (lit.,[7] 200 °C); δ($CDCl_3$–CD_3COCD_3, 60 MHz), 2.21 and 2.24 (each 3 H, s, Me), and 3.58 and 3.80 (each 3 H, s, OMe). On methylation as before this gave methyl 3,5-dichloro-6-(3,5-dichloro-2,4-dimethoxy-6-methylphenoxy)-4-methoxy-2-methylbenzoate (16) as needles (from methanol), m.p. 95—96 °C (lit.,[7] 97 °C); δ(CCl_4, 60 MHz) 2.22 and 2.30 (each 3 H, s, Me), and 3.40, 3.52, 3.79, and 3.87 (each 3 H, s, OMe). Hydrogenolysis of compound (4) as above gave compound (5) as prisms, m.p. and m.m.p. 136—137 °C, identical (mass and n.m.r. spectra and R_F values in three solvent systems) with that obtained from dechlorodiploicin.

Ullmann Synthesis of Methyl 6-(2,4-Dimethoxy-6-methylphenoxy)-4-methoxy-2-methylbenzoate (6).—The bromo-compound (7) [11] (2.7 g), the phenol (8) [12] (1.8 g), and dry finely divided potassium carbonate (3.0 g) were heated and stirred at 130 °C (bath) under dry nitrogen and copper(II) oxide (0.6 g) was then added and heating and stirring were continued for 12 h. The cooled mixture was diluted with ether and filtered through kieselguhr and the filtrate was washed in turn with dilute hydrochloric acid, dilute sodium hydroxide solution, water, and finally with saturated brine. The crude product was chromatographed over silica gel with 5—15% ethyl acetate–light petroleum as eluant which gave the diaryl ether (6) (2.3 g) as needles (from methanol), m.p. and m.m.p. 82—83 °C, identical (mass and n.m.r. spectra and R_F values in three solvent systems) with that prepared by degradation of dechlorodiploicin (Found: C, 65.8; H, 6.2. Calc. for $C_{19}H_{22}O_6$: C, 65.9; H, 6.4%).

Dechloro-O-methyldiploicin (9) *by Methylation of Dechlorodiploicin* (1).—Methylation of dechlorodiploicin (1) with iodomethane and potassium carbonate in *NN*-dimethylformamide as before gave the methyl ether (9) as needles (from dichloromethane–light petroleum), m.p. and m.m.p. 230—231.5 °C, identical (mass, n.m.r., and i.r. spectra and R_F values in three solvent systems) with the natural product (Found: C, 50.65; H, 3.15; Cl, 26.25. Calc. for $C_{17}H_{13}Cl_3O_5$: C, 50.6; H, 3.25; Cl, 26.35%).

Degradation of Buellolide (13).—Hydrogenolysis of buellolide as before gave *7-(2,4-dimethoxy-6-methylphenoxy)-5-methoxyisobenzofuran-1(3H)-one* (14) (60%) as prisms

(from chloroform–methanol), m.p. 146—147 °C (Found: M^+, 330.109 1. $^{12}C_{18}{}^{1}H_{18}{}^{16}O_6$ requires M, 330.110 3); δ($CDCl_3$, 90 MHz) 2.15 (3 H, s, $W_{\frac{1}{2}}$ 1.7 Hz, Me), 3.71, 3.74, and 3.80 (each 3 H, s, OMe), 5.20 (2 H, s, $W_{\frac{1}{2}}$ 2.5 Hz, CH_2), 6.00 and 6.50 (2 H, br AB, J 2.0 Hz, 6- and 4-H), and 6.35 and 6.41 (2 H, br AB, J 2.5 Hz, ArH). Irradiation at δ 5.20 sharpened the signals due to the 4- and 6-H, whilst irradiation at δ 2.15 sharpened the other AB system; *m/e* 331 (16%), 330 (64, M^+), 167 (14, $C_9H_{11}O_3$), 153 (16, $C_8H_9O_3$), 152 (14), 151 (100, $C_9H_{11}O_2$), and 139 (16).

7-Bromo-5-methoxyisobenzofuran-1(3H)-*one* (15).—A solution of the bromo-compound (7) [11] (6.0 g) in carbon tetrachloride (120 ml) was boiled over a 100 W tungsten lamp whilst bromine (3.83 g) in carbon tetrachloride (65 ml) was added dropwise over 2.5 h. After a further 0.5 h the cooled solution was diluted with ether and washed with water. The crude product in dry *NN*-dimethylformamide (100 ml) was stirred with anhydrous sodium acetate (20 g) for 20 h. The usual work-up gave an oil which was stirred at room temperature with sodium hydroxide (10 g) in water (75 ml) and methanol (250 ml) for 1 h. The solution was diluted with water and extracted with ether (3×); these extracts were discarded. The aqueous layer was acidified and extracted with ethyl acetate. The crude product crystallized from chloroform–methanol as needles (3.3 g) of the *phthalide* (15), m.p. 169 °C (Found: C, 44.65; H, 3.1; Br, 32.85%; M^+, 242, 244. $C_9H_7BrO_3$ requires C, 44.5; H, 2.9; Br, 32.85%; M, 242, 244); δ($CDCl_3$, 90 MHz) 3.90 (3 H, s, OMe), 5.17 (2 H, s, $W_{\frac{1}{2}}$ 2.5 Hz, CH_2), and 7.19 and 6.89 (2 H, br AB, J 2.1 Hz, ArH); irradiation at δ 5.17 sharpened the AB system.

Ullmann Synthesis of 7-(2,4-*Dimethoxy*-6-*methylphenoxy*)-5-*methoxyisobenzofuran*-1(3H)-*one* (14).—Ullmann reaction, as before, for 1.5 h between the bromophthalide (15) (2.5 g) and the phenol (8) [12] (1.75 g) gave a crude product which was chromatographed over silica gel with 10—40% ethyl acetate–light petroleum as eluant and gave first 7-*bromo*-3-(2,4-*dimethoxy*-6-*methylphenoxy*)-5-*methoxyisobenzofuran*-1(3H)-*one* (12) (130 mg) as needles (from dichloromethane–light petroleum), m.p. 185.5—187 °C (Found: Br, 19.55%; M^+, 408, 410. $C_{18}H_{17}BrO_6$ requires Br, 19.55%; M, 408, 410); δ($CDCl_3$, 90 MHz), 2.29 (3 H, s, $W_{\frac{1}{2}}$ 1.7 Hz, Me), 3.78, 3.90, and 3.94 (each 3 H, s, OMe), 6.30 and 6.40 (2 H, br AB, J 2.5 Hz, ArH), 6.52 (1 H, s, $W_{\frac{1}{2}}$ 1.8 Hz, 3-H), and 7.26 (2 H, s, $W_{\frac{1}{2}}$ 1.5 Hz, 4- and 6-H); irradiation at δ 7.26 sharpened the signal at δ 6.52, and irradiation at δ 2.29 sharpened the AB system; $\nu_{max.}$ ($CHCl_3$) 1 780 (C=O) and 1 610 (C=C) cm^{-1}. Further elution gave 7-(2,4-dimethoxy-6-methylphenoxy)-5-methoxyisobenzofuran-1(3*H*)-one (14) (1.50 g) which formed prisms (from chloroform–methanol), m.p. and m.m.p. 146—147 °C, identical (mass and n.m.r. spectra and R_F values in three solvent systems) with that obtained by degradation of buellolide (Found: C, 65.95; H, 5.45. Calc. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.5%).

4-*Chloro*-7-(3,5-*dichloro*-4,6-*dimethoxy*-2-*methylphenoxy*)-5-*methoxyisobenzofuran*-1(3H)-*one* (*Buellolide*) (13).—Sulphuryl chloride (1.863 g) in dichloromethane (45 ml) was added dropwise to a stirred solution of the diaryl ether (14) (914 mg) in dichloromethane (45 ml) and the mixture was then heated under reflux for 5 h. The usual work-up gave a residue which was chromatographed over silica gel with 15% ethyl acetate–light petroleum as eluant and this gave *buellolide* (13) (410 mg) which formed prisms (from dichloromethane–light petroleum), m.p. and m.m.p. 170—173 °C, identical (mass, n.m.r., and i.r. spectra and R_F values in three solvent systems) with the natural product (Found: C, 50.15; H, 3.45; Cl, 24.7. $C_{18}H_{15}Cl_3O_6$ requires C, 49.85; H, 3.5; Cl, 24.5%).

4,6-*Dichloro*-7-(3,5-*dichloro*-4,6-*dimethoxy*-2-*methylphenoxy*)-5-*methoxyisobenzofuran*-1(3H)-*one* (17) *from Diploicin* (2).—The diaryl ether (16) (111 mg) obtained by degradation of diploicin, as above, was heated under reflux in carbon tetrachloride (5 ml) during the dropwise addition of bromine (36.8 mg) in carbon tetrachloride (5 ml) over 1 h. After a further 0.5 h the usual work-up gave a crude product which was stirred for 15 h with anhydrous sodium acetate (1.0 g) in *NN*-dimethylformamide (3 ml). The crude product was stirred at 0 °C with sodium hydroxide (300 mg) in methanol (4 ml), dioxan (4 ml), and water (3 ml) for 3.5 h. The mixture was acidified and extracted with ethyl acetate and the crude product was subjected to preparative t.l.c. (2.5—5% ethyl acetate–light petroleum). The starting material (23.4 mg) was obtained from a fast moving band, and a slower moving band gave the *phthalide* (17) (6.2 mg) which formed prisms (from dichloromethane–light petroleum), m.p. 178—180 °C (Found: M^+, 465.955 9. $^{12}C_{18}{}^{1}H_{14}{}^{35}Cl_4{}^{16}O_6$ requires M, 465.954 4); δ(CCl_4, 60 MHz) 2.38 (3 H, s, Me), 3.50, 3.78, and 3.91 (each 3 H, s, OMe), and 4.99 (2 H, s, CH_2); $\nu_{max.}$ (CCl_4) 1 790 (C=O) cm^{-1}.

Degradation of Canesolide (18).—Hydrogenolysis of canesolide (18) as before gave 7-(2,5-*dimethoxy*-3-*methylphenoxy*)-5-*methoxyisobenzofuran*-1(3H)-*one* (19) (76%) which formed laths (from methanol), m.p. 185—187 °C (Found: M^+, 330.110 4. $^{12}C_{18}{}^{1}H_{18}{}^{16}O_6$ requires M, 330.110 3); δ($CDCl_3$, 90 MHz) 2.27 (3 H, apparent d, Me), 3.73, 3.75, and 3.76 (each 3 H, s, OMe), 5.21 (2 H, s, $W_{\frac{1}{2}}$ 2.6 Hz, CH_2), 6.16 (1 H, arm of br AB, J 2.0 Hz, ArH), and 6.57 (3 H, m, ArH).

2,5-*Dimethoxy*-3-*methylphenol* (22).—The phenol (20) [10] (13.0 g) was methylated in the usual way with methyl sulphate and potassium carbonate in acetone. The crude product was purified by chromatography over silica gel with 0—2.5% ethyl acetate–light petroleum as eluant which gave the methyl ether (21) (10.0 g) as an oil; δ(CCl_4, 60 MHz) 2.19 (3 H, s, Me), 3.59 and 3.68 (each 3 H, s, OMe), 4.90 (2 H, s, CH_2), 6.10 and 6.20 (2 H, AB, ArH), and 7.22 (5 H, s, Ph); *m/e* 258 (M^+). This product (21) (10.0 g) and 10% palladium–charcoal (0.5 g) were stirred under hydrogen in ethyl acetate (200 ml), containing concentrated hydrochloric acid (4 drops), until absorption ceased. Work-up in the usual fashion gave the phenol (22) (6.4 g) as an oil, b.p. 120—125 °C (bath) at 0.5 mmHg, which formed *prisms* (from light petroleum), m.p. 62—63 °C (Found: C, 64.35; H, 7.05%; M^+, 168. $C_9H_{12}O_3$ requires C, 64.25; H, 7.2%; M, 168); δ($CDCl_3$, 60 MHz) 2.20 (3 H, s, Me), 3.61 (6 H, s, 2 × OMe), 5.66 (1 H, s, OH), and 6.10 and 6.26 (2 H, AB, J 2.0 Hz, ArH).

Ullmann Synthesis of 7-(2,5-*Dimethoxy*-3-*methylphenoxy*)-5-*methoxyisobenzofuran*-1(3H)-*one* (19).—Ullmann reaction, as before, for 3 h between the phenol (22) (1.7 g) and the bromophthalide (15) (2.4 g) gave a crude product which was chromatographed over silica gel with 5—30% ethyl acetate–light petroleum as eluant. This afforded the diaryl ether (19) (0.8 g) as laths (from methanol), m.p. and m.m.p. 185—187 °C, identical (mass and n.m.r. spectra and R_F values in three solvent systems) with that obtained by degradation of canesolide (Found: C, 65.45; H, 5.5. Calc. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.5%).

Methyl 2-Bromo-4-hydroxy-6-methylbenzoate (26).—Benzyl 4-benzyloxy-2-bromo-6-methylbenzoate (23) (10.0 g),[10] potassium hydroxide (15 g), dimethyl sulphoxide (150 ml), and water (40 ml) were stirred at 90 °C for 14 h. The usual work-up gave the acid (24) which was stirred for 15 min with iodomethane (10 ml) and potassium carbonate (12 g) in *NN*-dimethylformamide (75 ml). The oily benzyl ether (25) (7.9 g), so obtained, and 10% palladium–charcoal (1.0 g) were stirred under hydrogen in ethyl acetate (100 ml), containing concentrated hydrochloric acid (10 drops), until absorption ceased. The usual work-up gave the *phenol* (26) (5.4 g) as needles (from dichloromethane–light petroleum), m.p. 104—105 °C (Found: C, 44.25; H, 3.65; Br, 32.55%; M^+, 244, 246. $C_9H_9BrO_3$ requires C, 44.1; H, 3.7; Br, 32.6%; *M*, 244, 246). The derived acetate (27) (pyridine—acetic anhydride) was obtained as an oil; δ($CDCl_3$, 60 MHz) 2.20 (3 H, s, MeCO), 2.28 (3 H, s, Me), 3.87 (3 H, s, OMe), and 6.33 and 7.09 (2 H, AB, *J* 2.0 Hz, ArH).

Methyl 4-Acetoxy-2-bromo-6-bromomethylbenzoate (28).—The acetate (27) (5.0 g) was heated under reflux in carbon tetrachloride (100 ml) over a 250 W incandescent lamp during the dropwise addition of bromine (2.8 g) in carbon tetrachloride (30 ml) during 1 h. After a further 15 min, work-up gave an oil which crystallized from dichloromethane–light petroleum as needles (3.8 g) of the *ester* (28), m.p. 125—127 °C (Found: C, 36.35; H, 2.8; Br, 43.9%; M^+, 364, 366, 368. $C_{11}H_{10}Br_2O_4$ requires C, 36.1; H, 2.75; Br, 43.65%; *M*, 364, 366, 368); δ($CDCl_3$, 60 MHz) 2.27 (3 H, s, MeCO), 3.91 (3 H, s, OMe), 4.39 (2 H, s, CH_2), and 7.09 and 7.27 (2 H, AB, *J* 2.0 Hz, ArH).

7-Bromo-5-hydroxyisobenzofuran-1(3H)-one (29).—The ester (28) (3.7 g) and anhydrous sodium acetate (10 g) were stirred at room temperature in dry *NN*-dimethylformamide (50 ml) for 20 h. The crude product was then stirred with sodium hydroxide (10 g) in methanol (75 ml) and water (100 ml) for 2 h. The usual work-up gave the *phthalide* (29) (2.3 g) as rods (from methanol), m.p. 264—266 °C (Found: C, 42.25; H, 2.3; Br, 35.2%; M^+, 228, 230. $C_8H_5BrO_3$ requires C, 41.95; H, 2.2; Br, 34.9%; *M*, 228, 230); δ($CDCl_3$–CD_3SOCD_3, 60 MHz) 5.09 (2 H, s, CH_2) and 6.78 and 7.08 (2 H, AB, *J* 2.0 Hz, ArH).

5-Benzyloxy-7-bromoisobenzofuran-1(3H)-one (30).—The phthalide (29) (2.2 g), benzyl bromide (3 g), and potassium carbonate (5 g) were stirred for 20 h in dry *NN*-dimethylformamide (50 ml) under dry nitrogen. The excess of benzyl bromide was removed from the crude product by steam distillation. The *phthalide* (30) (3.0 g) formed needles (from chloroform–methanol), m.p. 169—170 °C (Found: C, 56.65; H, 3.5; Br, 25.15%; M^+, 318, 320. $C_{15}H_{11}BrO_3$ requires C, 56.45; H, 3.45; Br, 25.05%; *M*, 318, 320); δ($CDCl_3$, 60 MHz) 5.09 (4 H, s, 2 × CH_2), 6.84 and 7.08 (2 H, AB, *J* 2.0 Hz, ArH), and 7.32 (5 H, s, Ph).

5-Hydroxy-7-(2,5-dimethoxy-3-methylphenoxy)isobenzofuran-1(3H)-one (32).—Ullmann reaction, as before, for 5 h between the phenol (22) (1.7 g) and the bromophthalide (30) (3.1 g) gave, after chromatography of the crude product over silica gel with 5—20% ethyl acetate–light petroleum as eluant, the diaryl ether (31) as an oil (1.3 g). This was stirred under hydrogen with 10% palladium–charcoal (300 mg), in ethyl acetate (100 ml), containing concentrated hydrochloric acid (2 drops), until absorption ceased. The usual work-up gave the product (32) (0.8 g) as *prisms* (from chloroform–methanol), m.p. 285—290 °C (decomp.) (Found: C, 64.65; H, 5.1%; M^+, 316. $C_{17}H_{16}O_6$ requires C, 64.55; H, 5.1%; *M*, 316); δ($CDCl_3$–CD_3SOCD_3, 60 MHz) 2.21 (3 H, s, Me), 3.61 and 3.65 (each 3 H, s, OMe), 5.10 (2 H, s, CH_2), 5.97 (1 H, arm of AB, *J* 2.0 Hz, ArH), and 6.41 (3 H, m, ArH).

We thank Dr. U. Engkaninan for the extraction of the lichen and the Australian Research Grants Committee for financial support.

[0/509 *Received*, 2nd *April*, 1980]

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