Structure of the Lichen Depsidone Variolaric Acid

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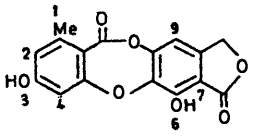
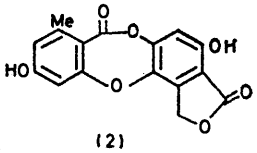
The structure of the lichen depsidone variolaric acid (1) advanced by Nolan in 1943 is unique among depsidones in possessing the diaryl ether linkage *ortho* to the hydroxy-group in ring B. Spectroscopic evidence and the synthesis of a degradation product have confirmed the originally assigned structure.

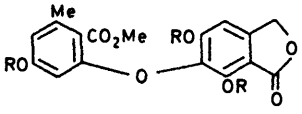
SINCE the structure of the lichen depsidone pannarin has been revised,[1] variolaric acid [2] is now unique among the known lichen depsidones in possessing the diaryl ether linkage *ortho* to the hydroxy-group of ring B. We therefore sought more concrete proof of the structure (1) for variolaric acid which was proposed by Nolan on the grounds of classical degradative evidence.[2] We considered the structure (2) was more likely since this possesses the diaryl ether linkage at the more usual position *para* to the hydroxy-group of ring B. This structure was rejected by Nolan [2] because the methanolysis product of variolaric acid, assigned structure (3), failed to give a blood-red colour with bleaching powder, whereas



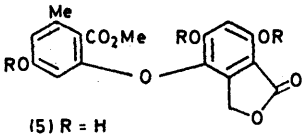
(1)



(2)



(3) R = H
(4) R = Me



(5) R = H
(6) R = Me

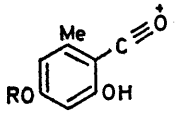
the product (5) derived from structure (2) should. Furthermore the methanolysis product gave a positive Gibb's test. In view of the dependence of the structural proof on colour tests, and in particular the unreliability of the Gibb's test, we favoured structure (2) for variolaric acid.

A small sample of variolaric acid was provided through the courtesy of Dr. S. Huneck. The n.m.r. spectrum of variolaric acid, previously recorded by Ollis,[3] was consistent with either structure (1) or (2). In keeping with the observation of Nolan [2] that variolaric acid gave a purple colour with iron(III) chloride, the i.r. spectrum ($CHCl_3$) of variolaric acid exhibited a band at 1 745 cm^{-1} attributable to the carbonyl stretching frequency of an *o*-hydroxyphthalide.[4] The mass spectrum of variolaric acid, as expected,[5] showed the ring A fragment ions (7) and (9).

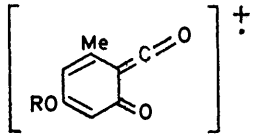
Methanolysis and subsequent methylation of variolaric acid gave a diaryl ether, m.p. 181—182°, the 90 MHz n.m.r. spectrum of which was in accord with ring A of structure (4) or (6) and which also indicated the presence of the lactonic ring. The mass spectrum of this product in addition to the ring A fragments (8) and (10) exhibited as the base peak the ring B fragment [1] of partial structure (11).

We therefore undertook the solution of the structural problem by the Ullmann synthesis of the methylated methanolysis products (4) and (6) corresponding to structures (1) and (2) for variolaric acid.

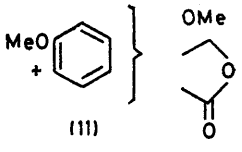
For the synthesis of the diaryl ether (6) we required the bromo-compound (12) available from previous work,[6] and the phenol (19). Photobromination of the bromo-compound (13) [7] gave the benzyl bromide (14) which was cyclised to the bromo-lactone (15).[4] This was conveniently debrominated by treatment with nickel–aluminium alloy and cold aqueous sodium hydroxide.[8] The resultant phthalide (16) [4] on formylation gave the aldehyde (17). The structure of the latter was proved by hydrogenation to the known methyl compound (18), the structure of which has been unequivocally proved by



(7) R = H
(8) R = Me



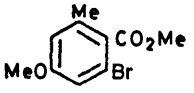
(9) R = H
(10) R = Me



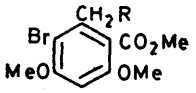
(11)

[1] D. A. Jackman, M. V. Sargent, and J. A. Elix, *J.C.S Perkin I*, 1975, 1979.
[2] D. Murphy, J. Keane, and T. J. Nolan, *Sci. Proc. Royal. Dublin Soc.*, 1943, **23**, 71.
[3] J. P. Devlin, C. P. Falshaw, W. D. Ollis, and R. E. Wheeler, *J. Chem. Soc.* (*C*), 1971, 1318.
[4] W. R. Allison and G. T. Newbold, *J. Chem. Soc.*, 1959, 3335; W. R. Logan and G. T. Newbold, *ibid.*, 1957, 1946.
[5] S. Huneck, C. Djerassi, D. Becher, M. Barber, M. von Ardenne, K. Steinfelder, and R. Tümmler, *Tetrahedron*, 1968, **24**, 2707.
[6] M. V. Sargent, P. Vogel, and J. A. Elix, preceding paper.
[7] J. R. Cannon, T. M. Cresp, B. W. Metcalf, M. V. Sargent, G. Vinciguerra, and J. A. Elix, *J. Chem. Soc.* (*C*), 1971, 3495.
[8] J. Santesson, *Acta Chem. Scand.*, 1970, **24**, 3373.

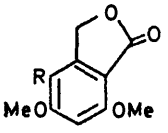
Logan and Newbold.[4] Baeyer–Villiger oxidation [9] of the aldehyde (17) and hydrolysis of the resultant formate



(12)



(13) R = H
(14) R = Br

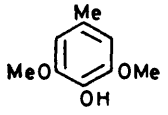


(15) R = Br
(16) R = H
(17) R = CHO
(18) R = Me
(19) R = OH

then gave the desired phenol (19). Ullmann reaction of the phenol (19) and the bromo-compound (12) gave the diaryl ether (6), m.p. 164—165°, different from that obtained by degradation of variolaric acid.

For the synthesis of the diaryl ether (4) the phenol (25) was required. The starting material was the phenol (20), available from previous work,[1] and was converted by formylation, acetylation, and oxidation into the acid (21) and thence into the ester (22). This on nuclear bromination and then photobromination furnished the benzyl bromide (23). Treatment of the latter with base gave the bromophthalide (24), which on debromination afforded the desired phenol (25). Ullmann reaction between the phenol (25) and the bromo-compound (12) then gave the diaryl ether (4), m.p. 181—182°, identical with the degradation product of variolaric acid.

Variolaric acid thus possesses the structure (1). Since it is the only depsidone which is known to occur in *Ochrolechia* spp. it has been suggested that its biosynthesis



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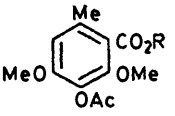
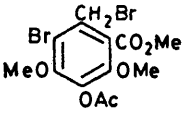
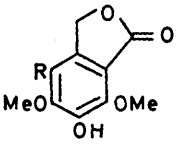


(21) R = H
(22) R = Me



(23)



(24) R = Br
(25) R = H

has evolved separately from that of the other orsellinic acid type depsidones.[10]

EXPERIMENTAL

General directions have been given previously.[1]

Variolaric Acid (3,6-*Dihydroxy*-8-*hydroxymethyl*-1-*methyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-7-*carboxylic Acid* γ-*Lactone*) (1).—The sample was in the form of needles, m.p. 295—297° (decomp.) [lit.,[2] 296° (decomp.)]; *m/e* 315 (19%), 314 (100, M^+), 286 (21), 285 (7), 270 (17), 269 (10), 259 (7), 258 (7), 257 (12), 242 (10), 241 (14), 202 (14), 201 (24), 200 (7), 196 (10), 195 (12), 164 (26), 163 (10), 157 (14), 152 (7), 151 (59), 150 (10), 147 (7), 145 (10), 143 (14), 141 (7), 135 (24), 134 (36), 129 (10), 128 (17), 127 (10), 124 (14), 122 (14), 121 (10), 120 (10), 115 (20), 108 (10), 107 (20), 106 (69), and 105 (20); $\nu_{max.}$ ($CHCl_3$) 1 745 (H-bonded lactone) and 1 715 (depsidone) cm^{-1}.

Degradation of Variolaric Acid (1).—Variolaric acid (1) (19.9 mg) was stirred with sodium methoxide [from sodium (160 mg)] and dry methanol (20 ml) under dry nitrogen for 8 h. The solution was poured into water and acidified with dilute hydrochloric acid. The solution was extracted with ethyl acetate and the extract was washed with saturated brine. The crude product was methylated with methyl iodide and potassium carbonate in *NN*-dimethylformamide. The crude product crystallised from dichloromethane–light petroleum as needles of 5,7-dimethoxy-6-(5-methoxy-2-methoxycarbonyl-3-methylphenoxy)phthalide (4), m.p. 181—182° (lit.,[2] 181—182°), τ (90 MHz) 3.30 (1 H, s, 4-H), 3.61 and 4.10 (2 H, ABdd, $J_{4',6'}$ 2.6 Hz, 4'- and 6'-H), 5.94, 6.10, 6.17, and 6.33 (each 3 H, s, OMe), and 7.64 (3 H, s, Me), *m/e* 389 (16%), 388 (71, M^+), 358 (8), 357 (33), 356 (12), 327 (7), 326 (5), 325 (21), 313 (9), 312 (5), 311 (18), 298 (5), 297 (6), 283 (6), 269 (7), 225 (5), 224 (21, 209 (5), 195 (6), 194 (15), 193 (100), 179 (7), 165 (18), 164 (37), 163 (16), 162 (29), 151 (7), 150 (6), 149 (18), 148 (6), 139 (5), 137 (5), 136 (12), 135 (16), 134 (5), 127 (5), 125 (8), 123 (7), 121 (11), 120 (9), 119 (7), 113 (9), 111 (15), 110 (5), 109 (11), 107 (6), and 105 (7); $\nu_{max.}$ ($CHCl_3$) 1 755 (lactone) and 1 720 cm^{-1} (ester).

Methyl 3-*Bromo*-2-*bromomethyl*-4,6-*dimethoxybenzoate* (14).—This was prepared by an adaptation of the method of Logan and Newbold.[4] A solution of methyl 5-bromo-2,4-dimethoxy-6-methylbenzoate (13) [7] (28.23 g) in carbon tetrachloride (250 ml) was boiled under reflux over a 100 W tungsten lamp while bromine (15.68 g) in carbon tetrachloride (55.3 ml) was added dropwise. The solution was then heated under reflux for 1 h, cooled, and washed with aqueous sodium disulphite and with saturated brine. The product (14) (35.8 g, 99%) was sufficiently pure for the next step. A sample crystallised from dichloromethane–light petroleum formed needles, m.p. 116—118° (lit.,[4] 118.5—119°), τ 3.55 (1 H, s, ArH) 5.34 (2 H, s, CH_2), and 6.08, 6.12, and 6.17 (each 3H, s, OMe).

4-*Bromo*-5,7-*dimethoxyphthalide* (15).—This was prepared from the foregoing dibromo-compound (14) by the method of Logan and Newbold.[4] The crude product (78%) had m.p. 243—245° (lit.,[4] 246—248°).

5,7-*Dimethoxyphthalide* (16).—A stirred solution of the phthalide (15) (22.0 g) in dioxan (470 ml) and aqueous sodium hydroxide (2N; 470 ml) was cooled to 0 °C and treated in portions with nickel–aluminium alloy (32.8 g), and stirring was continued at 0 °C for a further 15 min. The suspension was filtered and the acidified filtrate was extracted with ethyl acetate; the extract was washed with saturated brine. Removal of the solvent gave the product (16) (13.5 g, 86%), m.p. 149—150° (lit.,[4] 151—153°), τ (90 MHz) 3.51br (1 H, m, 4-H), 3.58br (1 H, m, 6-H), 4.85br (2 H, s, CH_2), and 6.06 and 6.11 (each 3 H, s, OMe).

[9] I. M. Godfrey, M. V. Sargent, and J. A. Elix, *J.C.S. Perkin I*, 1974, 1353.

[10] C. F. Culberson, 'Chemical and Botanical Guide to Lichen Products,' University of North Carolina Press, Chapel Hill, 1969, p. 36.

4-Formyl-5,7-dimethoxyphthalide (17).—A stirred solution of the phthalide (16) (12.0 g) and dichloromethyl methyl ether (42.6 g) in dichloromethane (450 ml) was treated dropwise over 1 h at 0 °C with a solution of titanium(IV) chloride (71.4 g) in dichloromethane (152 ml). The solution was then stirred at 0 °C for 0.5 h and at room temperature for 3 h. An excess of cold dilute hydrochloric acid was added to the stirred solution and the precipitated product was separated by filtration. The organic phase was separated from the filtrate and was washed with saturated brine. Removal of the solvent gave more crude product. The combined crude product was crystallised from methanol and formed *needles* (10.8 g, 79%), m.p. 277—279° (Found: C, 59.4; H, 4.5%; M^+, 222. $C_{11}H_{10}O_5$ requires C, 59.45; H, 4.55%; *M*, 222), $\nu_{max.}$ ($CHCl_3$) 1 750 (lactone) and 1 660 cm^{-1} (CHO).

5,7-Dimethoxy-4-methylphthalide (18).—The phthalide (17) (155 mg) and 10% palladised charcoal (200 mg) were stirred under hydrogen in acetic acid (100 ml) until absorption ceased. The usual work-up gave the phthalide (18) (131 mg, 90%) as needles (from methanol), m.p. 203—203.5° (lit.,[4] 202—203°) (Found: C, 63.2; H, 5.7%; M^+, 208. Calc. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.8%; *M*, 208), τ 3.59 (1 H, s, ArH), 4.92 (2 H, s, CH_2), 6.03 and 6.08 (each 3 H, s, OMe), and 7.98 (3 H, s, Me).

4-Hydroxy-5,7-dimethoxyphthalide (19).—A solution of the aldehyde (17) (10.8 g) and *m*-chloroperbenzoic acid (85%, 16.6 g) in acetic acid (450 ml) was stirred at 90—100 °C (bath) for 2 h. The residue left on removal of the solvent under diminished pressure was dissolved in dichloromethane and was washed exhaustively with saturated aqueous sodium hydrogen carbonate, and with saturated brine. The crude product was dissolved in warm methanol (750 ml) and stirred at room temperature under nitrogen for 1 h with aqueous 10% sodium hydroxide (200 ml). The solution was acidified with dilute hydrochloric acid and then most of the methanol was removed under diminished pressure. The residue was extracted exhaustively with warm dichloromethane and the extract was washed with saturated brine. The crude product was crystallised from methanol and afforded needles (6.4 g, 63%) of the *phenol* (19), m.p. 246—247° (Found: C, 57.0; H, 4.85%; M^+, 210. $C_{10}H_{10}O_5$ requires C, 57.15; H, 4.8%; *M*, 210), τ [$(CD_3)_2SO$] 3.31 (1 H, s, ArH), 4.89 (2 H, s, CH_2), and 6.08 and 6.13 (each 3 H, s, OMe).

5,7-Dimethoxy-4-(5-methoxy-2-methoxycarbonyl-3-methylphenoxy)phthalide (6).—The bromo-compound (12) [6] (3.8 g), the phenol (19) (2.5 g), and dry finely divided potassium carbonate (3.5 g) in dry pyridine (15 ml) were stirred and heated gradually to 130 °C (bath) under dry nitrogen. Copper(II) oxide (0.75 g) was then added and the mixture was stirred and heated at 150 °C (bath) for 20 h. The cooled mixture was diluted with hot chloroform and filtered through kieselguhr. The filtrate was washed with dilute hydrochloric acid and with saturated brine. The crude product was chromatographed over silica gel with 10—30% ethyl acetate–benzene as eluant. The *diaryl ether* (6) (2.6 g, 57%) formed needles (from methanol), m.p. 164—165° (Found: C, 61.6; H, 5.2%; M^+, 388. $C_{20}H_{20}O_8$ requires C, 61.85; H, 5.2%; *M*, 388), τ (90 MHz) 3.44 (1 H, s, 6-H), 3.56 and 4.01 (2 H, ABq, $J_{4',6'}$ 2.6 Hz, 4'- and 6'-H), 5.98, 6.07, 6.12, and 6.30 (each 3 H, s, OMe), and 7.65 (3 H, s, Me), $\nu_{max.}$ ($CHCl_3$) 1 760 (lactone) and 1 725 cm^{-1} (ester).

3-Hydroxy-2,4-dimethoxy-6-methylbenzaldehyde.—Titanium(IV) chloride (188 g) in dry dichloromethane (380 ml) was added dropwise over 15 min to a stirred solution of the phenol (20) [1] (59.8 g) and dichloromethyl methyl ether (112.5 g) in dry dichloromethane (600 ml) at 0 °C. The mixture was then stirred at 0 °C for 0.5 h and at room temperature for 0.5 h. The stirred solution was then treated with cold dilute hydrochloric acid and the organic phase was separated and washed with saturated brine. The n.m.r. spectrum of the crude product indicated it to be 3-formyloxy-2,4-dimethoxy-6-methylbenzaldehyde. The crude formate was therefore stirred in methanol (600 ml) at 0 °C under nitrogen and treated with an ice-cold aqueous 10% solution of sodium hydroxide (310 ml). After 0.5 h the solution was acidified with dilute hydrochloric acid and most of the methanol was removed under reduced pressure. The residue was extracted with ethyl acetate and the extract was washed with water and with saturated brine. The crude product crystallised from cyclohexane and afforded needles (45.2 g, 65%) of the *aldehyde*, m.p. 100—103° (Found: C, 61.2; H, 5.95%; M^+, 196. $C_{10}H_{12}O_4$ requires C, 61.2; H, 6.15%; *M*, 196), τ −0.43 (1 H, s, CHO), 3.50 (1 H, s, ArH), 4.44br (1 H, s, OH), 6.02 and 6.06 (each 3 H, s, OMe), and 7.44 (3 H, s, Me).

3-Acetoxy-2,4-dimethoxy-6-methylbenzaldehyde.—Acetylation of the foregoing phenol with pyridine and acetic anhydride (1 h; 90 °C) in the usual way gave the *acetate* (98%) as plates (from cyclohexane), m.p. 105—107° (Found: C, 60.6; H, 6.10%; M^+, 238. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%; *M*, 238), τ −0.43 (1 H, s, CHO), 3.40 (1 H, s, ArH), 6.09 and 6.11 (each 3 H, s, OMe), 7.39 (3 H, s, ArMe), and 7.63 (3 H, s, OAc).

Methyl 3-Acetoxy-2,4-dimethoxy-6-methylbenzoate (22).—A solution of potassium permanganate (107.5 g) and magnesium sulphate monohydrate (106.5 g) in water (2 l) was added dropwise to a stirred solution of the aldehyde (44.5 g) in acetone (1 370 ml) at such a rate that the reaction temperature was 20—25 °C. The solution was then stirred at room temperature until t.l.c. indicated the absence of starting material when it was cooled (ice–salt) and clarified by the passage of sulphur dioxide. The acidified mixture was then extracted with ethyl acetate and the extract was washed exhaustively with saturated aqueous sodium hydrogen carbonate. The acidified washings were then extracted with ethyl acetate and the extract was washed with saturated brine. The crude product crystallised from toluene as prisms (24.1 g, 50%) of *3-acetoxy-2,4-dimethoxy-6-methybenzoic acid* (21), m.p. 162—167° (Found: C, 57.0; H, 5.55%; M^+, 254. $C_{12}H_{14}O_6$ requires C, 56.7; H, 5.55%, *M*, 254). The acid in methanol was treated with an excess of ethereal diazomethane which gave the *ester* (22) (94%) as prisms (from pentane), m.p. 66—67° (Found: C, 58.4; H, 6.1%, M^+, 268. $C_{13}H_{16}O_6$ requires C, 58.2; H, 6.0%; *M*, 268), τ (CCl_4) 3.55 (1 H, s, ArH), 6.19 (3 H, s, OMe), 6.27 (6 H, s, 2 × OMe), and 7.67 (6 H, s, 2 × Me).

Methyl 3-Acetoxy-5-bromo-6-bromomethyl-2,4-dimethoxybenzoate (23).—Bromine (11.1 g) in acetic acid (50 ml) was added over 10 min to a stirred mixture of the ester (22) (18.6 g), anhydrous sodium acetate (20 g), and acetic acid (60 ml). After 15 h the usual work up gave methyl 3-acetoxy-5-bromo-2,4-dimethoxy-6-methylbenzoate (22.6 g, 94%) as an oil, τ (CCl_4) 6.17, 6.21, and 6.26 (each 3 H, s, OMe), and 7.68 and 7.72 (each 3 H, s, Me). Bromine (11.5 g) in carbon tetrachloride (100 ml) was added over 1 h to a solution of the ester (22.6 g) in carbon tetrachloride (250 ml) which was boiled under reflux over a 100 W tungsten lamp. After 20 h more bromine (3.6 g) in carbon tetrachloride (50 ml) was added over 1 h and boiling under reflux was

continued for a further 20 h. Work up in the usual way gave the product (27.6 g, 99%). A sample crystallised from light petroleum as prisms of the *ester* (23), m.p. 89—90° (Found: C, 36.65; H, 3.35; Br, 37.1%; M^+, 424/426/428. $C_{13}H_{14}BrO_6$ requires C, 36.65; H, 3.3; Br, 37.5%, *M*, 424/426/428), τ (CCl_4) 5.32 (2 H, s, CH_2), 6.08, 6.17, and 6.20 (each 3 H, s, OMe), and 7.70 (3 H, s, OAc).

4-*Bromo*-6-*hydroxy*-5,7-*dimethoxyphthalide* (24).—The crude ester (23) (4.3 g) and aqueous sodium hydroxide (2N; 185 ml) were stirred and heated under gentle reflux for 2 h under nitrogen. The cooled acidified solution was extracted with ethyl acetate and the extract was washed with saturated brine. The crude product crystallised from methanol as needles (2.16 g, 74%) of the *phthalide* (24), m.p. 159—161° (Found: C, 41.8; H, 3.35; Br, 27.35, 27.45%; M^+, 288/290. $C_{10}H_9BrO_5$ requires C, 41.55; H, 3.15; Br, 27.65%; *M*, 288/290), τ 3.89br (1 H, OH), 4.90 (2 H, s, CH_2), and 5.73 and 5.94 (each 3 H, s, OMe).

6-*Hydroxy*-5,7-*dimethoxyphthalide* (25).—The bromophthalide (24) (6.64 g) in aqueous sodium hydroxide (2N; 200 ml) was stirred and cooled to 0 °C and treated with nickel–aluminium alloy (10 g) in portions over 0.5 h. After a further 0.5 h at 0 °C work-up as before gave the *phthalide* (25) (4.40 g, 92%) as clusters of needles (from dichloromethane–light petroleum), m.p. 134.5—135° (Found: C, 57.3; H, 4.75%; M^+, 210. $C_{10}H_{10}O_5$ requires C, 57.15; H, 4.8%; *M*, 210), τ 3.30 (1 H, s, ArH), 3.72br (1 H, OH), 4.83 (2 H, s, CH_2), and 5.84 and 6.01 (each 3 H, s, OMe).

Ullmann Reaction between the Bromo-compound (12) *and the Phenol* (25).—Ullmann reaction, as before, between the bromo-compound (12) and the phenol (25) gave, after the usual work-up and chromatography, the diaryl ether (4) (5%) as needles (from dichloromethane–light petroleum); m.p. and mixed m.p. 181—182° (Found: C, 61.7; H, 5.4%, M^+, 388. Calc. for $C_{20}H_{20}O_8$: C, 61.85; H, 5.2%; *M*, 388), identical (R_F in several systems; mass and n.m.r. spectra) with the degradation product.

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