A quinonoid naphthopyranone as a model for the synthesis of the pigment xylindein. Photochemical formation of the lactone ring

Robin G.F. Giles, Michael K. Reuben, and Gregory H.P. Roos

3-Propyl-3,4,5,10-tetrahydronaphtho[2,3-*c*]pyran-1,5,10(1*H*)-trione (**5**) has been synthesized with a view to determining a satisfactory pathway to its 7,9-dihydroxy-analogue (**4**), which it is hoped will ultimately provide a route to the extended quinonoid pigment, xylindein. A key step in the reaction sequence is the photo-rearrangement of 1,4-dimethoxy-*trans*-3-pent-1-enylnaphthalene-2-carboxylic acid (**11**) into the related δ-lactone (**12**) having the required ring system. Subsequent silver(II) oxide oxidative demethylation affords the target quinone (**5**).

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3-Propiel-3,4,5,10-tetrahidronafto[2,3-*c*]piraan-1,5,10(1*H*)-trioon (**5**) is gesintetiseer om 'n effektiewe roete na die 7,9-dihidroksi-analoog (**4**) te vind. Hierdie verbinding (**4**) word beskou as 'n moontlike tussenstap in die roete wat na die vergrote kinonoidiese pigment xilindeïen sal lei. Die sleutelstap in die reaksie-reeks is die foto-omskakeling van 1,4-dimetoksi-*trans*-3-pent-1-enielnaftaleen-2-karboksielsuur (**11**) na die verwante δ-laktoon (**12**) wat die benodigde ringsisteem bevat. Oksidatiewe demetilering van **12** met silwer(II)-oksied gee die gewensde kinoon (**5**).

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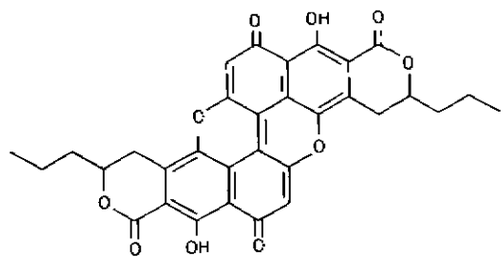
The naturally occurring pigment xylindein has been assigned the extended quinonoid structure (**1**).[1,2] In considering a possible synthesis of the fused ring system, it was noted that Cameron *et al.*[3] had effected the anaerobic coupling of the aphid degradation product (**2**) to afford xylaphin (**3**), which differs from xylindein only in the construction of the two heterocyclic rings. It therefore appeared that a likely synthetic precursor of xylindein would be the quinonoid naphthopyranone (**4**). We describe here a synthesis of the dideoxy-analogue (**5**) which possesses the required ring system.



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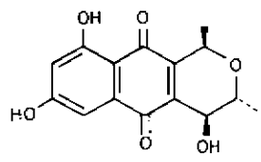

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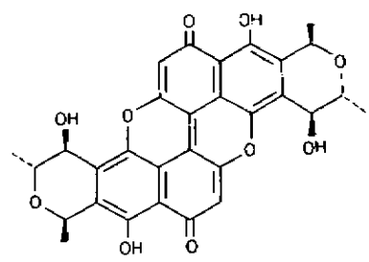

3

2-Bromonaphthoquinone (**6**)[4] was alkylated with hexanoic acid in the presence of silver nitrate and

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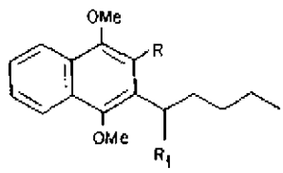
ammonium persulphate to afford the quinone (7) (90%), which was in turn converted into the hydroquinone dimethyl ether (8) (95%) by reductive methylation. Bromination of this naphthalene with *N*-bromosuccinimide in the presence of di-t-butyl peroxide cleanly yielded the product (9) of benzylic bromination; the ^{1}H n.m.r. spectrum of this material showed the benzylic proton as a pair of triplets centred at δ 5,93 (J 7 Hz) owing to restricted rotation about the naphthalene–benzylic carbon bond through steric crowding. Variable temperature measurements in toluene-d_8 afforded a coalescence temperature of 70 °C. Without further purification, the benzylic bromide was boiled in lutidine, which gave the *trans*-olefin (10) as the sole product (88% from 8). Treatment of the *trans*-olefin (10) with butyl-lithium in ether followed by carbon dioxide gave rise to the unsaturated acid (11) (76%). The stereochemistry about the double bond was clearly indicated by the coupling constant (16 Hz) of the olefinic protons in compound (11).

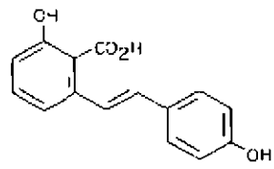
Formation of the lactone ring system from the unsaturated acid (11) was accomplished using a novel photochemical ring closure. The acid (11) was irradiated in solution in cyclohexane through quartz using a vycor filter to afford the lactone (12) (40%). The n.m.r. spectrum of this fused δ-lactone showed *inter alia* the methine proton as a multiplet at δ 4,42 coupled to the two benzylic protons, which each appeared as a pair of doublets at δ 3,37 (J 2,5 and 16 Hz) and 2,81 (J 11 and 16 Hz). Double irradiation at the C(3) methylene frequency collapsed the multiplet at δ 4,42 into a pair of doublets (J 2,5 and 11 Hz), whereas irradiation of the methine proton collapsed the benzylic protons into a geminally coupled pair of doublets (J 16 Hz), thus providing confirmation of the assignment of structure (12). For comparison purposes, the alternative γ-lactone (13) was prepared by the following sequence. The bromonaphthalene (8) was converted into the naphthalenic acid (14) (92%) by treatment with butyl-lithium, followed by carbon dioxide. The product (14) was brominated with *N*-bromosuccinimide in the presence of di-t-butyl peroxide to afford the intermediate bromo-acid (15). On boiling the crude product in lutidine, it gave rise to the lactone (13) (70% from 14) by intramolecular displacement of bromide ion by the neighbouring carboxylate group. The ^{1}H n.m.r. spectrum of this lactone exhibited the signal for the methine proton as a double doublet at δ 5,68 (J 3 and 8 Hz), coupled to a high-field multiplet centred at δ 2,28.

While the photochemical formation of a lactone ring in the above manner appears to have no literature precedent, a not unrelated thermal ring closure has been reported[5] for the conversion of the stilbene acid, hydrangea acid (16), into hydrangeol (17). However, on heating the unsaturated acid (11), decarboxylation occurred to afford 2-pent-1-enyl-1,4-dimethoxynaphthalene (18) as the sole product observed, identical with material obtained as a by-product in the conversion of the *trans*-bromo-olefin (10) into the acid (11). It may be conjectured that in the transformation 16→17 an alternative mechanism may be operating, for example *via* a quinone methide.

Lactone (12) was converted into the quinone (5) (80%) by oxidative demethylation using silver(II) oxide.[6]



14 R = CO_2H, R_1 = H
15 R = CO_2H, R_1 = Br
19 R = R_1 = H



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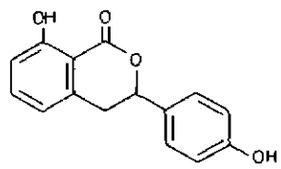

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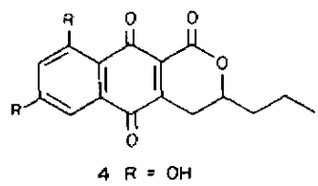
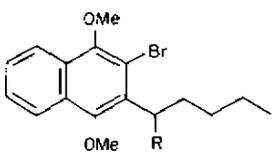
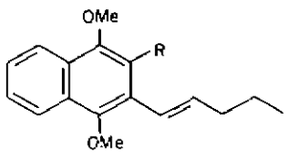


4 R = OH
5 R = H

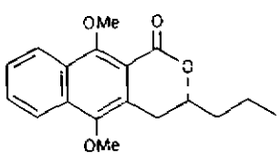
6 R = H
7 R = $(CH_2)_4CH_3$



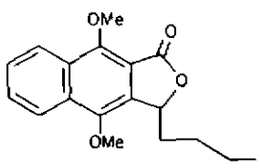
8 R = H
9 R = Br



10 R = Br
11 R = CO_2H
18 R = H



12



13

Experimental

N.m.r. spectra were measured on a Varian XL-100 instrument for solutions in [^{2}H]-chloroform with tetramethylsilane as internal reference. Dry column chromatography was performed using Merck Kieselgel 60 (70–230 mesh). Light petroleum refers to the fraction, b.p. 60–80 °C.

2-Bromo-3-pentyl-1,4-naphthoquinone (7)

A mixture of 2-bromo-1,4-naphthoquinone (6)[4] (550 mg), silver nitrate (400 mg), and hexanoic acid (400 mg) in water–acetonitrile (12:12 ml) was heated at 60–65 °C with vigorous stirring and treated over 1 h with a freshly prepared aqueous solution of ammonium peroxodisulphonate (800 mg in 10 ml water). The dark solution was stirred for a further 10 min at the same temperature, then cooled and the excess of acid was neutralized with solid sodium carbonate. The mixture was filtered, extracted with ether (2 × 25 ml), and the organic layer was dried and evaporated. The crude orange residue was chromatographed (ethyl acetate–light petroleum, 1:19) to afford the *product* (640 mg, 90%) as yellow needles, m.p. 90–91 °C (from methylene chloride light petroleum), $\nu_{max.}$ (CCl_4) 1670, 1596, and 1470 cm^{-1}, δ 0,92 (3H, t, J 6 Hz, CH_3), 1,16–1,80 (6H, m, 3 × CH_2), 2,85 (2H, t, J 7 Hz, 1′-CH_2),

7,64—7,84 (2H, m, 6- and 7-H), and 8,00—8,12 (2H, m, 5- and 8-H) (Found: C, 58,4; H, 4,85. Calc. for $C_{15}H_{15}BrO_2$: C, 58,65; H, 4,9%).

2 *Bromo* 1,4 *dimethoxy* 3-*pentylnaphthalene* (8)

The quinone (7) (1,50 g) in ether (50 ml) was shaken with sodium dithionite (an excess) in water (50 ml). The organic phase was separated, dried, and evaporated. The solid residue was immediately taken up in dry acetone (50 ml) and treated under nitrogen with anhydrous potassium carbonate (5 g) and dimethyl sulphate (4 ml). The mixture was heated under reflux with vigorous stirring for 8 h. The solid was filtered off and washed with acetone. The combined filtrate and washings were evaporated, and the oily residue was dissolved in ether and washed with a concentrated ammonia solution (5 ml), water, dilute hydrochloric acid, and saturated brine. Upon work-up, the residue was chromatographed (ethyl acetate-light petroleum, 1:49) to afford the *product* (1,56 g, 95%), m.p. 72—73 °C (from methanol), δ 0,83—1,05 (3H, m, CH_3), 1,30—1,84 (6H, m, $3\times CH_2$), 2,97 (2H, t, J 7 Hz, 1'-CH_2), 3,93 (3H, s, OCH_3), 3,98 (3H, s, OCH_3), 7,45—7,60 (2H, m, 6- and 7-H), and 8,00—8,19 (2H, m, 5- and 8-H)(Found: C, 60,2; H, 6,0. Calc. for $C_{17}H_{21}BrO_2$: C, 60,5; H, 6,3%).

2-*Bromo*-1,4-*dimethoxy*-trans-3-*pent*-1-*enylnaphthalene* (10)

A solution of the dimethyl ether (8) (270 mg) in dry carbon tetrachloride (15 ml) was treated with *N*-bromosuccinimide (160 mg) and a catalytic amount of di t-butyl peroxide, and the mixture was heated under gentle reflux for 2 h. The solution was cooled, filtered, and reduced to afford the crude dibromide (9), δ 0,76—1,02 (3H, m, CH_3), 1,22—1,60 (4H, m, $2\times CH_2$), 2,50—2,77 (2H, m, 2'-CH_2), 3,98 (6H, s, $2\times OCH_3$), 5,80 and 6,06 (1H, $2\times$t, J 7 Hz, 1'-CH), 7,46—7,64 (2H, m, 6 and 7-H), and 8,03—8,19 (2H, m, 5 and 8 H). Without further purification, the material was heated under reflux in 2,6-lutidine (15 ml) for 2,5 h. The solution was cooled, filtered, and evaporated under reduced pressure. The dark residue was chromatographed (ethyl acetate-light petroleum, 1:39) to afford the *product* as colourless needles (235 mg, 88%), m.p. 62—63 °C (from methanol), δ 1,02 (3H, t, J 7 Hz, CH_3), 1,42—1,78 (2H, m, 4'-CH_2), 2,20—2,44 (2H, m, 3'-CH_2), 3,80 (3H, s, OCH_3), 3,97 (3H, s, OCH_3), 6,45—6,70 (2H, m, 1'- and 2'-H), 7,46—7,64 (2H, m, 6 and 7 H), and 8,02—8,22 (2H, m, 5- and 8-H)(Found: C, 60,7; H, 5,6. Calc. for $C_{17}H_{19}BrO_2$: C, 60,9; H, 5,7%).

1,4-*Dimethoxy*-trans-3-*pent*-1-*enylnaphthalene*-2-*carboxylic acid* (11)

A solution of the olefinic bromide (10) (960 mg) in dry ether (75 ml) was treated at room temperature under nitrogen with one equivalent of n-butyl-lithium (in hexane) and the resulting mixture was stirred for 0,5 h. This solution was added to an excess of solid carbon dioxide and stirred until ambient temperature was reached. Aqueous 5% sodium hydroxide (100 ml) was then carefully added. The aqueous layer was collected, acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The organic phase was dried and evaporated to afford the *product* (650 mg, 76%), m.p. 101—103 °C (from methanol), δ 0,99 (3H, t, J 7 Hz, CH_3), 1,34—1,74 (2H, m, 4'-CH_2), 2,16—2,2 (2H, m, 3'-CH_2), 3,88 (3H, s, OCH_3), 4,05 (3H, s, OCH_3), 6,36 (1H, d×t, J 6 and 15 Hz, 2'-H), 6,67 (1H, d, J 15 Hz, 1'-H), 6,80 (1H, br s, -OH), 7,50—7,66 (2H, m, 6- and 7 H), and 8,05—8,24 (2H, m, 5- and 8-H)(Found: C, 72,2; H, 6,5. Calc. for $C_{18}H_{20}O_4$: C, 72,0; H, 6,65%). Work-up of the neutral ethereal layer gave the oily 1,4 dimethoxy-*trans* 2-pent-1-enylnaphthalene (18) (150 mg, 20%), δ 1,00 (3H, t, J 6,5 Hz, CH_3), 1,38—1,70 (2H, m, 4'-CH_2), 2,14—2,44 (2H, m, 3'-CH_2), 3,88 (3H, s, OCH_3), 3,98 (3H, s, OCH_3), 6,32 (1H, d×t, J 7 and 16 Hz, 2'-H), 6,95 (1H, d, J 16 Hz, 1'-H), 6,91 (1H, s, 3-H), 7,32—7,58 (2H, m, 6- and 7-H), and 7,98—8,30 (2H, m, 5 and 8 H).

5,10-*Dimethoxy*-3-*propyl*-2,3-*dihydronaphtho*[2,3-c]*pyran*-(1H)1-*one* (12)

The acid (11) (100 mg) in cyclohexane (60 ml) was irradiated under nitrogen for 1,5 h through quartz fitted with a vycor sleeve. The solvent was evaporated, the residue was dissolved in ethyl acetate, and any acidic material was removed by washing with 1% aqueous sodium hydroxide. After work-up, the residue was subjected to thin layer chromatography on silica gel (ethyl acetate-light petroleum, 1:9) to afford the *product* (28 mg, 40% based on unrecovered starting material), m.p. 98—99 °C (from methanol), δ 0,96 (3H, deformed t, J 7 Hz, CH_3), 1,40—1,95 (4H, m, 1'- and 2'-CH_2), 2,81 (1H, dd, J 11 and 16 Hz, 4-H), 3,37 (1H, dd, J 2,5 and 16 Hz, 4-H), 3,88 (3H, s, OCH_3), 4,10 (3H, s, OCH_3), 4,42 (1H, m, 3-H), 7,44—7,80 (2H, m, 7- and 8-H) and 8,03—8,42 (2H, m, 6- and 9-H)(Found: C, 71,4; H, 6,7%; M^+, 300,13526. Calc. for $C_{18}H_{20}O_4$: C, 72,0; H, 6,7%, M, 300,13614). Work-up of the acidic fraction afforded a residue which on chromatography gave starting material (30 mg).

2-*Propyl*-3,4,5,10-*tetrahydronaphtho*[2,3-c]*pyran*-1,5,10(1H) *trione* (5)

The lactone (12) (100 mg) and silver(II) oxide (165 mg) were stirred at room temperature in dioxan (5 ml). Nitric acid (6M, 0,4 ml) was added to initiate the reaction and stirring was continued for 1 min. The reaction was halted by addition of chloroform-water (13:3 ml). The organic phase was separated and the water layer was washed with a further amount of chloroform. The combined organic extracts were washed with a small quantity of water, dried, and evaporated to give the *product* (72 mg, 80%), m.p. 129—130 °C (from methanol), δ 0,99 (3H, t, CH_3), 1,35—2,11 (4H, m, 1'- and 2'-CH_2), 2,59 (1H, dd, J 11 and 18 Hz, 4-H), 3,21 (1H, dd, J 3 and 18 Hz, 4-H), 4,51 (1H, m, 3-H), 7,61—7,91 (2H, m, 7- and 8 H), and 7,97—8,13 (2H, m, 6- and 9-H)(Found: C, 70,95; H, 5,2. Calc. for $C_{16}H_{14}O_4$: C, 71,1; H, 5,2%).

1,4-*Dimethoxy*-3-*pentylnaphthalene* 2 *carboxylic acid* (14)

A solution of the bromide (8) (1,35 g) in dry ether (60 ml) was treated with n-butyl-lithium and solid carbon dioxide as described for compound (11). Work-up as before gave, from the aqueous layer, the *product* (1,11 g, 92%), m.p. 89,5—90,5 °C (from light petroleum), δ 0,92 (3H, deformed t, J 7 Hz, CH_3), 1,24—1,90 (6H, $2\times$m, $3\times CH_2$), 2,78—3,04 (2H, m, 1'-CH_2), 3,92 (3H, s, OCH_3), 4,06 (3H, s, OCH_3), 7,44—7,66 (2H, m, 6- and 7 H), 8,00—8,20 (2H, m, 5- and 8 H), and 10,80 (1H, br s, OH)(Found: C, 71,3; H, 7,3. Calc. for $C_{18}H_{22}O_4$: C, 71,5; H, 7,3%).

Work-up of the ethereal layer afforded 1,4-dimethoxy-2-pentylnaphthalene (19) (72 mg, 7%), δ 0,92 (3H, deformed t, J 6,5 Hz, CH_3), 1,16—1,90 (6H, $2\times$m, $3\times CH_2$), 2,70—2,92 (2H, m, 1'-CH_2), 3,89 (3H, s, OCH_3), 3,98 (3H, s, OCH_3), 6,63 (1H, s, 3-H), 7,34—7,62 (2H, m, 6 and 7 H), and 7,96—8,30 (2H, m, 5- and 8 H).

3-*Butyl*-4,9-*dimethoxy*-1,3-*dihydronaphtho*[2,3-c]*furan*-1-*one* (13)

The acid (14) (150 mg) was brominated with *N*-bromosuccinimide and di t-butyl peroxide as for compound (9). Work-up as before gave the bromide (15), δ 0,78—1,04 (3H, m, CH_3), 1,22—1,64 (4H, m, $2\times CH_2$), 2,34—2,70 (2H, m, 2'-CH_2), 4,09 (6H, s, $2\times OCH_3$), 5,66 (1H, t, J 7 Hz, 1'-H), 7,40—7,74 (2H, m, 6- and 7-H), 8,02—8,24 (2H, m, 5- and 8-H), and 10,94 (1H, br s, OH). Without further purification, the bromide was heated under reflux in 2,6-lutidine (10 ml) for 1 h. The dark solution was cooled, filtered, and evaporated, and the residue was taken up in ethyl acetate. This organic phase was washed with a small quantity of dilute hydrochloric acid, and then extracted with dilute sodium hydroxide. Work-up of the organic layer gave the *product* (104 mg, 70%), m.p. 107—108 °C (from methanol), δ 0,78—1,04 (3H, m, CH_3), 1,22—1,54 (4H, m, $2\times CH_2$), 1,80 and 2,28 (2H, $2\times$m, 1'-CH_2), 3,98 (3H, s, OCH_3), 4,30 (3H, s, OCH_3), 5,68 (1H, dd, J 3 and 8 Hz, 3-H), 7,44—7,80 (2H, m, 6- and 7-H), and 8,05—8,48 (2H, m, 5- and 8-H)(Found: M^+, 300,13818. Calc. for $C_{18}H_{20}O_4$: M, 300,13605). Acidification and work-up of the basic aqueous layer gave a small amount of the *trans* olefinic acid (11) identical with that prepared earlier.

Acknowledgements

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References

1 (a) G.M. Blackburn, A.H. Nielsen, and Lord Todd, *Proc. Chem. Soc.*, 1962, 327; (b) G.M. Blackburn, D.E.V. Ekong, A.H. Nielsen, and Lord Todd, *Chimia*, 1965, **19**, 208.

2 R.L. Edwards and N. Kale, *Tetrahedron*, 1965, **21**, 2095.

3 G.M. Blackburn, D.W. Cameron, and H.W.-S. Chan, *J. Chem. Soc. (C)*, 1966, 1836.

4 S.M. McElvain and E.L. Engelhardt, *J. Am. Chem. Soc.*, 1944, **66**, 1077.

5 Y. Asahini and J. Asano, *Ber. Dtsch. Chem. Ges.*, 1930, **63**, 2059.

6 C.D. Snyder and H. Rapoport, *J. Am. Chem. Soc.*, 1972, **94**, 227.