Model studies towards xylindein precursors

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Alternative synthetic methodology has been investigated for the preparation of 3-propyl-3,4,5,10-tetrahydronaphtho[2,3-*c*]pyran-1,5,10(1*H*)-trione (**3**) with the view to making it more generally applicable to the synthesis of precursors *viz.* (**2**) to the extended pigment xylindein (**1**). Indications are that the more highly oxygenated naphthalene systems react less favourably towards free radical alkylations and mild oxidation than the simpler cases.

Alternatiewe sintetiese metodologie is ondersoek vir die voorbereiding van 3-propiel-3,4,5,10-tetrahidronafto-[2,3-*c*]piraan-1,5,10(1*H*)-trioon (**3**), met die doel om dit van meer algemene toepassing te maak vir voorlopers nl. (**2**) tot die uitgebreide pigment xilindeïen (**1**). Aanduidings is dat hoe meer die naftaleenkern geoksigeneerd is, hoe swakker reageer dit met betrekking tot vryradikaalalkilerings en matige oksidasie vergeleke met meer eenvoudige gevalle.

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The naturally occurring quinonoid pigment xylindein (**1**) is widely distributed in nature[1] and has had its structure elucidated.[2,3] As a consequence of certain anaerobic coupling reactions of aphid degradation products by Blackburn *et al.*,[3] it was noted that xylindein-type systems could thereby be generated. This observation led Giles *et al.*[4] to postulate that the lactone (**2**) could be a likely precursor to xylindein (**1**), and led to the development of a method for the synthesis of the 7,9-dideoxy analogue (**3**).

In attempting to extend the earlier methodology of Giles *et al.*[4] to tetraoxygenated systems, certain major difficulties were encountered. Thus, when the 1,4,5,7-tetramethoxynaphthalene (**4**) was brominated with *N*-bromosuccinimide under a wide variety of free radical bromination conditions, only the 8-bromo derivative (**5**) was isolated.[5] All attempts to brominate the benzylic position failed, owing to the competing reactivity of position 8 in the naphthalene nucleus. Consequently, a new route to the model lactone (**3**) was sought with the view to extending this methodology in the synthesis of **2**.

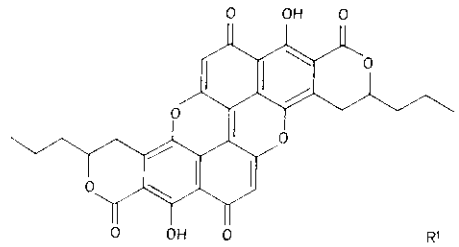
All attempts to acylate 1,4-dimethoxynaphthalene with trifluoroacetic anhydride failed in our hands. However, treatment with premixed trifluoroacetic anhydride and glacial acetic acid[6] gave rise to an 80% yield of the corresponding 2-acyl derivative (**6**).[7] This ease of acylation suggested a viable alternative synthetic route towards the synthesis of lactone (**3**) and more generally, lactone (**2**).

Thus, oxidation of ketone (**6**) with aqueous sodium hypochlorite produced a high yield (98%) of the corresponding naphthoic acid (**7**), which was identified by a broad band in the i.r. spectrum at 3200—2300 cm^{-1} and in the ^1H n.m.r. spectrum, by a D_2O exchangeable proton at δ 9,10. Conversion of the acid (**7**) into the corresponding acid chloride proceeded smoothly with thionyl chloride at room temperature. The product was not isolated, but was used immediately for further elaboration to the amide (**8**) by treatment with aqueous methylamine.

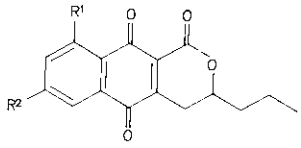
Oxidative demethylation of amide (**8**) with silver(II) oxide and nitric acid afforded an excellent yield of the amide quinone (**9**). It was necessary to have the molecule at this oxidation level since it was now possible to effect a free radical alkylation regiospecifically at position 3.[8] Thus, quinone (**9**) was treated with 3-hydroxyhexanoic acid in the presence of silver nitrate and potassium persulphate under nitrogen to yield the 3-alkylated quinone (**10**) in 52% yield. The quinone carbonyl groups were clearly evident in the i.r. spectrum by the presence of a strong band at 1665 cm^{-1}. The ^1H n.m.r. spectrum of this quinone showed *inter alia* the *N*-methyl group as a doublet at δ 2,85 (*J* 5 Hz) and the α-methylene-hydrogens as a separate multiplet at δ 2,45, while the β-methine proton appeared as a multiplet at δ 3,80 deshielded by the attached oxygen. All attempts to form the desired lactone (**3**) by pyrolysis of quinone (**10**) failed, and resulted in extensive decomposition. This problem was successfully overcome in the following way.

Reductive methylation of quinone (**10**) yielded the naphthalene dimethyl ether (**11**) which, upon pyrolysis under nitrogen, afforded the δ-lactone (**12**), identical in all respects to the material previously prepared by Giles *et al.*[4] Oxidative demethylation of lactone (**12**) led to the isolation of the target δ-lactone (**3**), also identical with the material previously prepared.[4]

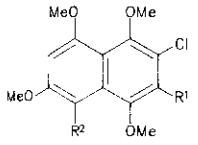
Attention was then focussed on the synthesis of tetra-oxygenated analogues of the series just investigated, and thus the analogue (**13**) was chosen since the starting materials were available.



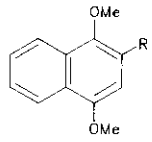
(1)



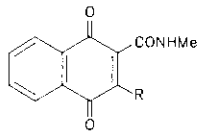
(2) $R^1 = R^2 = OH$
(3) $R^1 = R^2 = H$



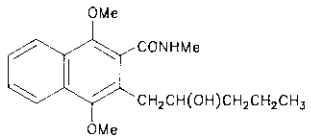
(4) $R^1 = C_5H_{11}$; $R^2 = H$
(5) $R^1 = C_5H_{11}$; $R^2 = Br$



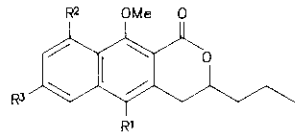
(6) R = $COCH_3$
(7) R = COOH
(8) R = CONHMe



(9) R = H
(10) R = $CH_2CH(OH)CH_2CH_2CH_3$



(11)

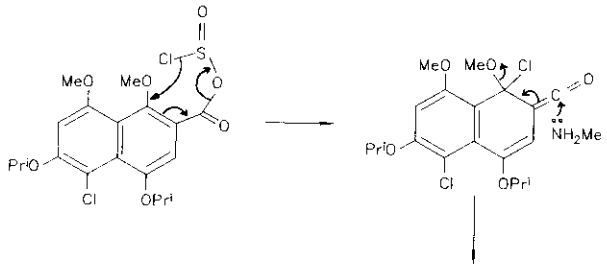


(12) R^1 = OMe ; $R^2 = R^3$ = H
(13) $R^1 = R^3$ = OPr^i ; R^2 = OMe

To this end, the trifluoroacetylnaphthol (**14**)[9] was methylated under mildly alkaline conditions to the tetramethyl ether (**15**) in high yield (86%). Care had to be taken so as not to disrupt the trifluoroacetyl function at that stage. Mild methanolic alkaline hydrolysis of the trifluoroacetyl group of **15** afforded an excellent yield of the corresponding acid (**16**). Treatment of this acid with hot thionyl chloride, followed by treatment with aqueous methylamine as previously described, produced a single product of higher R_F than starting material and in high yield. The ^{1}H n.m.r. spectrum of the product showed *inter alia* a three-proton doublet at δ 3,04 (*J* 5 Hz) for the N–CH_3 group and two sharp one-proton singlets at δ 7,33 and 7,53 as well as a broad one-proton singlet centred at δ 7,90. The i.r. spectrum confirmed the amide functionality by an N–H band at 3300 cm^{-1} and the amide I band at 1640 cm^{-1}. Elemental analysis showed that two chlorine atoms had been introduced into the molecule. Furthermore, since only one methoxy signal was evident in the ^{1}H n.m.r. spectrum at δ 3,73, the structure assigned for this product is the dichloronaphthalene (**17**). The more shielded signal at δ 7,33 was assigned to 6-H while the less shielded signal at δ 7,53 was assigned to 2-H.

A possible mechanism for this aromatic substitution reaction is illustrated in Scheme 1.

Scheme 1



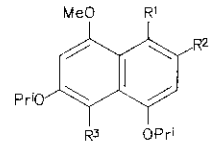
17

Lowering the temperature in the treatment of the naphthalenic acid (**16**) with thionyl chloride was also unsuccessful since, in this instance, the sole product isolated in high yield was the 8-chloronaphthamide (**18**). This again illustrated the highly reactive nature of position 8 of these naphthalenic systems supporting some earlier findings by Giles *et al.*[10]

The precise mechanism of the aromatic chlorination at position 8 would be speculative at this stage, since the thionyl chloride was distilled prior to use and, although the mode of attack should be by electrophilic chlorine, the origin of such a species is unknown.

In viewing alternative routes towards the synthesis of amide (**19**) it was found that this could best be achieved by first converting the naphthoic acid (**16**) into the corresponding methyl ester (**20**) by the mild method employing iodomethane in the presence of potassium carbonate in dry acetone, followed by ammonolysis with aqueous methylamine. By this method, a high yield [85% from acid (**16**)] of amide (**19**) was achieved and the product was identified by three prominent signals in the ^{1}H n.m.r. spectrum. Thus, the signal for 6-H appeared as a shielded doublet (*J* 2,5 Hz) at δ 6,53, while that of 8-H appeared as the less shielded doublet (*J* 2,5 Hz) at δ 7,20. The signal for 2-H appeared as a singlet at δ 7,47, being the most deshielded of the three, owing to the anisotropic effect of the adjacent amide group. Similar trends were observed for the ester (**20**) (see Experimental).

Oxidative demethylation of the amide (**19**) with silver(II) oxide and nitric acid produced the desired quinone (**21**) in poor yield (24%), in contrast to the excellent yield (92%) obtained in the analogous synthesis of quinone (**9**) from amide (**8**). The signals for the aromatic protons in quinone (**21**) were definitive in the ^{1}H n.m.r spectrum, with that of 6-H appearing as a doublet (*J* 2,5 Hz) at δ 6,70 while that of 8-H also appeared as a doublet (*J* 2,5 Hz), but at δ 6,80, showing the expected deshielding by the *peri* carbonyl group. The signal for the quinonoid



(14) R^1 = OH ; R^2 = $COCF_3$; R^3 = H
(15) R^1 = OMe ; R^2 = $COCF_3$; R^3 = H
(16) R^1 = OMe ; R^2 = COOH ; R^3 = H
(17) R^1 = R^3 = Cl ; R^2 = CONHMe
(18) R^1 = OMe ; R^2 = CONHMe ; R^3 = Cl
(19) R^1 = OMe ; R^2 = CONHMe ; R^3 = H
(20) R^1 = OMe ; R^2 = CO_2Me ; R^3 = H
(23) R^1 = OMe ; R^2 = $CONMe_2$; R^3 = H

(21) R^1 = CONHMe ; R^2 = H
(22) R^1 = CONHMe ; R^2 = $CH_2CH(OH)CH_2CH_2CH_3$
(24) R^1 = $CONMe_2$; R^2 = H

2-H appeared as a singlet at δ 7,68. Both carbonyl bands were clearly evident in the i.r. spectrum, with the amide I band at 1685 cm^{-1} and the quinone carbonyl band at 1665 cm^{-1}.

In attempting the next step in the synthetic scheme, certain difficulties were encountered. It was found that in spite of precautions taken in performing the free radical alkylation on quinone (**21**), the best yield of the 2-alkylated product (**22**) was a mere 14%. Additionally, the product proved to be very unstable. The position of attachment was clearly at C(2) since the only evident aromatic proton signals in the ^1H n.m.r. spectrum were 6-H, which appeared as a doublet (*J* 2,5 Hz) at δ 6,55, while 8-H appeared as a doublet (*J* 2,5 Hz) at δ 7,05, again deshielded by the *peri* carbonyl group.

It was hoped that by employing the tertiary amide (**23**) as a precursor to the corresponding quinone (**24**), a greater degree of stability might be introduced into the quinonoid system. Thus, amide (**19**) was treated with sodium hydride and iodomethane to afford an excellent yield (93%) of the tertiary amide (**23**).

Oxidative demethylation under the most carefully controlled conditions produced the desired quinone (**24**), but in an extremely poor yield (14%).

Thus, although an initially acceptable alternate synthetic strategy had been devised for the synthesis of δ-lactones of the type (**3**), introduction of oxygens at positions 5 and 7 cause the whole naphthalenic system to be so electron-rich as to impede both nuclear oxidations as well as free radical alkylations, and hence new synthetic strategies to the elusive δ-lactone (**2**) will have to be sought.

Experimental

^1H N.m.r. spectra were recorded in deuteriochloroform on either a Varian EM 360, Varian XL–100 or Varian XL–200 spectrometer. Mass spectra were recorded on a VG Micromass 16F mass spectrometer at 70 eV and an ion source temperature of 180—220°. High resolution mass spectra were recorded on a Varian MAT 311 A spectrometer. I.r. spectra were measured as Nujol mulls on a Pye–Unicam SP3–300 spectrometer and calibrated against the 1601 cm^{-1} peak of polystyrene film. Microanalyses were carried out on a Heraeus CHN–RAPID analyser. Column chromatography was carried out using Merck Kieselgel (70—230 mesh). Light petroleum refers to the fraction of boiling point 60—80°.

1,4-*Dimethoxy*-2-*naphthoic acid* (**7**)

Ketone (**6**)[7] (1 g; 4,35 mmol) in dioxane (40 ml) was added dropwise over a period of 1 h to a stirred solution of sodium hypochlorite (10—14% *m/v*; 90 ml) at 75 °C. After addition, the resulting solution was stirred at 75°C for a further 75 min, after which the solution was cooled and sodium disulphite (5 g) in water (30 ml) was slowly added. The solution was washed with dichloromethane to remove any organic material. Thereafter, the aqueous phase was acidified (dilute HCl), and the solid material was filtered off and washed with water. This solid was then chromatographed using ethyl acetate – light petroleum (3:17) as eluent. In this way, the pure *naphthoic acid* (**7**) was obtained (720 mg; 72%), m.p. 167—168°C (acetone – light petroleum); ν_{max} 3200—2300 (OH) and 1675 (C=O) cm^{-1}; δ 4,03 (3H, s, OCH_3), 4,10 (3H, s, OCH_3), 7,30 (1H, s, 3-H), 7,5—8,35 (4H, m, ArH), and 9,1 (1H, br. s, D_2O exchangeable, COOH) (Found: C, 67,1; H, 5,25. Calc. for $C_{13}H_{12}O_4$: C, 67,25; H, 5,15%). It was found that using sodium hypobromite improved the yield to 98%.

N-*Methyl*-1,4-*dimethoxy*-2-*naphthamide* (**8**)

The acid (**7**) (3,8 g; 16,38 mmol) was stirred with thionyl chloride (40 ml) for 40 min at room temperature, after which the excess of reagent was removed under reduced pressure. The oily residue was immediately taken up in dry acetone (10 ml) and slowly added to a stirred solution of cold (5°C) methylamine (40% aqueous; 30 ml) and stirring was continued for 1 h. Thereafter, the reaction mixture was poured into water (150 ml) and dilute hydrochloric acid was added until the mixture became acidic to litmus. During this period, a solid was precipitated which was filtered off and washed with water. Chromatography using an eluent of ethyl acetate – light petroleum (1:3) afforded the *amide* (**8**) as colourless crystals (3,80 g; 88%), m.p. 121—122°C (chloroform – light petroleum); ν_{max} 3300 (NH) and 1635 (C=O) cm^{-1}; δ 3,05 (3H, d, *J* 5 Hz, NCH_3), 3,90 (3H, s, OCH_3), 4,00 (3H, s, OCH_3), 7,40 (1H, s, 3-H), and 7,45—8,35 (5H, m, ArH and NH) (Found: C, 68,55; H, 6,15; N, 5,75. Calc. for $C_{14}H_{15}NO_3$: C, 68,55; H, 6,10; N, 5,70%).

N-*Methyl*-2-*carboxamido*-1,4-*naphthoquinone* (**9**)

To a mixture of the amide (**8**) (600 mg; 2,30 mmol) and silver(II) oxide (1,52 g; 12,26 mmol) in dioxane (10 ml) at room temperature was added nitric acid (6M, 4 ml) over a period of 5 min. Thereafter, the reaction was quenched by the addition of a chloroform–water mixture (26:6 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane.

Removal of the solvent from the dried ($MgSO_4$) extracts produced a residue which was chromatographed with eluent ethyl acetate – light petroleum (2:3), on a short column protected from the light, to yield the *quinone* (**9**) (490 mg; 92%), m.p. 127—128°C (chloroform – light petroleum), ν_{max} 3350 (NH), 1680 (CONHMe), and 1665 (C=O of quinone) cm^{-1}; δ 3,05 (3H, d, *J* 5 Hz, NMe), 7,6—8,2 (5H, m, 3-H and ArH), and 8,65 (1H, br. s, NH) (Found: C, 66,75; H, 4,35; N, 6,50. Calc. for $C_{12}H_9NO_3$: C, 66,98; H, 4,19; N, 6,51%).

N-*Methyl*-3-(2′-*hydroxypentyl*)-2-*carboxamido*-1,4-*naphthoquinone* (**10**)

A mixture of quinone (**9**) (518 mg; 2,41 mmol) and 3-hydroxyhexanoic acid (795 mg; 6,02 mmol) in acetonitrile (30 ml) containing silver nitrate (200 mg; 1,08 mmol) in distilled water (3 ml) was treated dropwise with potassium persulphate (1,3 g; 4,81 mmol) in distilled water (30 ml) under nitrogen over a period of 40 min at 78°C (oil bath). After addition, stirring was continued for a further 90 min at 78°C and the reaction mixture was poured into water (200 ml). Ether extraction and chromatography of the product with eluent ethyl acetate – light petroleum (1:1) gave the *alkylated quinone* (**10**) as a yellow oil (377 mg; 52%), ν_{max} (neat) 3430 (OH and NH), 1725 (CONHMe), and 1665 (C=O of quinone) cm^{-1}; δ 0,90 (3H, t, *J* 6,5 Hz, 5′-CH_3), 1,2—1,8 (4H, m, 3′- and 4′-CH_2), 2,45 (2H, m, 1′-CH_2), 2,85 (3H, d, *J* 5 Hz, NMe), 3,80 (1H, m, 2′-H), 5,20 (1H, br. s, D_2O exchangeable, OH), 7,01 (1H, br. s, NH), and 7,5—8,0 (4H, m, ArH) (M^+, 301,1283. Calc. for $C_{17}H_{19}NO_4$: M^+, 301,1314).

N-*Methyl*-1,4-*dimethoxy*-3-(2′-*hydroxypentyl*)-2-*carboxamidonaphthalene* (**11**)

The quinone (**10**) (320 mg; 1,06 mmol) was reductively methylated under the usual conditions,[4] to afford the *dimethyl ether* (**11**) as a colourless oil (260 mg; 74%), ν_{max} (neat) 3370br (OH and NH), 1635 (amide I) cm^{-1}; δ 0,90 (3H, distorted t, *J* 6,5 Hz, 5′-CH_3), 1,3—1,6 (4H, m, 3′- and 4′-CH_2), 2,65 (2H, m, 1′-CH_2), 2,95 (3H, d, *J* 5 Hz, NCH_3), 3,80 (6H, s, 2×OCH_3), 3,90 (1H, m, 2′-H), 6,55 (1H, br. s, NH), 7,3—7,6 (2H, m, 6- and 7-H), 7,75—8,20 (2H, m, 5- and 8-H) (Found: C, 68,70; H, 7,70; N, 4,10%, M^+, 331,1812. Calc. for $C_{19}H_{25}NO_4$: C, 68,88; H, 7,55; N, 4,23%, *M*, 331,1783).

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

Amide (**11**) (140 mg; 0,423 mmol) was pyrolysed in a nitrogen atmosphere at 170—200°C (oil bath) for 5 h. The cooled material was chromatographed in the dark using ethyl acetate – light petroleum (1:1) as eluent to afford the δ-lactone (**12**) (51 mg; 37%), m.p. 105—106°C (from methanol) (lit.,[4] 98—99°C). The material was identical spectroscopically to that published in the literature.[4]

4,5-*Dimethoxy*-1,7-*di*(2-*propyloxy*)-3-*trifluoroacetylnaphthalene* (**15**)

The naphthol (**14**)[9] (300 mg; 0,777 mmol) in dry acetone (20 ml) was treated with iodomethane (6,8 g; 48 mmol) and potassium carbonate (1 g; 7,25 mmol), and the mixture was vigorously stirred and heated under reflux in a nitrogen atmosphere for 3,5 h. The reaction mixture was cooled and filtered, and evaporation of the volatiles gave an oily residue which was chromatographed using ethyl acetate – light petroleum (1:4) as eluent to afford the *product* (**15**) (267 mg; 86%), m.p. 89—91°C (from methanol); ν_{max} 1605 cm^{-1}; δ 1,43 [12H, d, *J* 6,5 Hz, 2×$CH(CH_3)_2$], 3,83 (3H, s, OCH_3), 3,98 (3H, s, OCH_3), 4,73 [2H, m, 2×$CH(CH_3)_2$], 6,60 (1H, d, *J* 2,5 Hz, 6-H), 6,95 (1H, s, 2-H), and 7,27 (1H, d, *J* 2,5 Hz, 8-H) (Found: C, 59,90; H, 5,60%; M^+, 400,1514. Calc. for $C_{20}H_{23}F_3O_5$: C, 60,00; H, 5,75%; M^+, 400,1497).

4,5-*Dimethoxy*-1,7-*di*(2-*propyloxy*)-3-*naphthoic acid* (**16**)

Compound (**15**) (800 mg; 2 mmol) in methanol (15 ml) was added over a period of 15 min to a stirred solution of aqueous potassium hydroxide (12% *w*/*v*; 30 ml) at 70°C (oil bath). Stirring was continued for a further 40 min, after which the dark solution was poured into water (200 ml) and extracted with the dichloromethane (2×50 ml). The aqueous layer was acidified with dilute HCl and extracted with dichloromethane (4×80 ml). The dried ($MgSO_4$) organic extract was stripped of solvent to yield the *acid* (**16**) (571 mg; 82%), m.p. 127—128 °C (dichloromethane – light petroleum); ν_{max} 3300—2500br, 1660, and 1610 cm^{-1}; δ 1,43 [12H, d, *J* 6,5 Hz, 2×$CH(CH_3)_2$], 3,93 (3H, s, OCH_3), 4,00 (3H, s, OCH_3), 4,71 [2H, m, 2×$CH(CH_3)_2$], 6,60 (1H, d, *J* 3 Hz, 6-H), 7,23 (1H, d, *J* 3 Hz, 8-H), 7,37 (1H, s, 2-H), and 9,80 (1H, br. s, D_2O exchangeable, COOH) (Found: C, 65,50; H, 6,90. Calc. for $C_{19}H_{24}O_6$: C, 65,52; H, 6,90%).

4,8-*Dichloro*-5-*methoxy*-1,7-*di*(2-*propyloxy*)-3-N-*methylnaphthamide* (**17**)

The naphthoic acid (**16**) (400 mg; 1,15 mmol) was treated with distilled thionyl chloride (20 ml) and the solution was heated under reflux for 1 h. Evaporation of the excess of thionyl chloride under reduced pressure gave an oily residue which was taken up in dry acetone (5 ml). This solution was slowly added to cold (5°C) aqueous methylamine (40%; 30 ml) and the mixture was stirred for 3 h and then poured into water (100 ml). Extraction of this aqueous mixture with dichloromethane (4×40 ml) gave a residue, upon drying of the organic layer ($MgSO_4$) and evaporation of the solvent, which was chromatographed using ethyl acetate – light petroleum (3:7) as eluent to afford the *product* (**17**) (320 mg; 70%), m.p. 146—147°C (from 2-propanol); ν_{max} 3300 and 1640 cm^{-1}; δ 1,43 [12H, d, *J* 6,5 Hz, 2×$CH(CH_3)_2$], 3,04 (3H, d, *J* 5 Hz, NCH_3), 3,73 (3H, s, OCH_3), 4,67 [2H, m, 2×$CH(CH_3)_2$], 7,33 (1H, s, 6-H), 7,53 (1H, s, 2-H), and 7,90 (1H, br. s, NH) (Found: C, 56,95; H, 5,80; N, 3,55. Calc. for $C_{19}H_{23}Cl_2NO_4$: C, 57,01; H, 5,75; N, 3,50%).

8-Chloro-4,5-dimethoxy-1,7-di(2-propyloxy)-3-N-methylnaphthamide (**18**)

Naphthoic acid (**16**) (125 mg; 0,359 mmol) was stirred with distilled thionyl chloride (3 ml) at room temperature for 30 min. The excess of thionyl chloride was evaporated under reduced pressure to produce an oily residue which was taken up in dry acetone (4 ml) and slowly added to cold (5°C) aqueous methylamine (40%; 10 ml). The mixture was stirred for 18 h and worked up as for compound (**15**). Chromatography using ethyl acetate – light petroleum (1:1) gave an oily unstable *product* (**18**) (132 mg; 93%); ν_{max} (ncat) 3300 and 1635 cm^{-1}; δ 1,43 [12H, d, *J* 6,5 Hz, 2 × CH(CH_3)$_2$], 3,03 (3H, d, *J* 5 Hz, NCH_3), 3,75 and 3,95 (each 3H, s, OCH_3), 4,67 [2H, m, 2 × C*H*(CH_3)$_2$], 6,70 (1H, s, 6-H), 7,57 (1H, s, 2-H), and 8,10 (H, br. s, NH) (Found: C, 60,40; H, 6,20; N, 3,20. Calc. for $C_{20}H_{26}ClNO_5$: C, 60,69; H, 6,57; N, 3,54%).

Methyl-4,5-dimethoxy-1,7-di(propyloxy)-3-naphthoate (**20**)

Naphthoic acid (**16**) (440 mg; 1,26 mmol) in dry acetone (40 ml) was treated with iodomethane (10 g; 70 mmol) and potassium carbonate (2 g; 14,5 mmol), and vigorously stirred and heated under reflux for 1,5 h. Filtration of the cooled reaction mixture and evaporation of the volatiles gave a residue which was chromatographed using ethyl acetate – light petroleum (3:7) as eluent to afford the *ester* (**20**) (450 mg; 98%) as an oil, ν_{max} (neat) 1700 and 1610 cm^{-1}; δ 1,43 [12H, d, *J* 6,5 Hz, 2 × CH(CH_3)$_2$], 3,85 3,93, and 3,95 (each 3H, s, 2 × OCH_3 and CO_2CH_3), 4,67 [2H, septet, *J* 6,5 Hz, 2 × C*H*(CH_3)$_2$], 6,52 (1H, d, *J* 2,5 Hz, 6-H), 7,13 (1H, s, 2-H), and 7,18 (1H, d, *J* 2,5 Hz, 8-H) (Found: C, 66,35; H, 7,35. Calc. for $C_{20}H_{26}O_6$: C, 66,30; H, 7,18%).

4,5-Dimethoxy-1,7-di(2-propyloxy)-3-N-methylnaphthamide (**19**)

The ester (**20**) (165 mg; 0,456 mmol) in acetone (3 ml) was added to aqueous methylamine (40%; 20 ml) and the resulting solution was stirred for 16 h at 50°C (oil bath), then poured into water (100 ml). Exhaustive extraction with dichloromethane and removal of the dried ($MgSO_4$) solvent yielded a residue that was chromatographed using ethyl acetate – light petroleum (3:2) as eluent to afford the desired *amide* (**19**) (143 mg; 87%), m.p. 116—117°C (from dichloromethane – light petroleum); ν_{max} 3310 and 1620 cm^{-1}; δ 1,42 [12H, d, *J* 6,5 Hz, 2 × CH(CH_3)$_2$], 3,03 (3H, d, *J* 5 Hz, NCH_3), 3,77 (3H, s, OCH_3), 3,93 (3H, s, OCH_3), 4,73 [2H, septet, *J* 6,5 Hz, 2 × C*H*(CH_3)$_2$], 6,53 (1H, d, *J* 2,5 Hz, 6-H), 7,20 (1H, d, *J* 2,5 Hz, 8-H), 7,47 (1H, s, 2-H), and 8,10 (1H, br. s, NH) (Found: C, 66,60; H, 7,45; N, 3,90. Calc. for $C_{20}H_{27}NO_5$: C, 66,48; H, 7,48; N, 3,89%).

5-Methoxy-7-(2-propyloxy)-3-N-methylcarboxamido-1,4-naphthoquinone (**21**)

Nitric acid (6M; 2 ml) was added to a stirred mixture of the amide (**19**) (50 mg; 0,138 mmol) and silver(II) oxide (86 mg; 0,693 mmol) in dioxane (4 ml) over a period of 4 min. The reaction was halted by the addition of a dichloromethane – water mixture (1:3) (20 ml) and was then diluted further with water (80 ml) and extracted with dichloromethane (3 × 50 ml). The dried ($MgSO_4$) extract was stripped of solvent to yield a residue that was chromatographed on a short column and eluted with ethyl acetate – light petroleum (7:3) to afford the *quinone* (**21**) (10 mg; 24%), m.p. 175—177°C (dichloromethane – light petroleum); ν_{max} 3300, 1685, and 1665 cm^{-1}; δ 1,43 [6H, d, *J* 6,5 Hz, CH(CH_3)$_2$], 2,97 (3H, d, *J* 5 Hz, NCH_3), 3,95 (3H, s, OCH_3), 4,73 [1H, septet, *J* 6,5 Hz, C*H*(CH_3)$_2$], 6,70 (1H, d, *J* 2,5 Hz, 6-H), 6,80 (1H, d, *J* 2,5 Hz, 8-H), 7,68 (1H, s, 2-H), and 8,90 (1H, br. s, NH) (Found: C, 63,00; H, 5,90; N, 4,40. Calc. for $C_{16}H_{17}NO_5$: C, 63,37; H, 5,61; N, 4,62%).

2-(2-Hydroxypentyl)-5-methoxy-7-(2-propyloxy)-3-N-methylcarboxamido-1,4-naphthoquinone (**22**)

Quinone (**21**) (83 mg; 0,274 mmol) in acetonitrile (30 ml) containing 3-hydroxyhexanoic acid (68 mg; 0,515 mmol) and silver nitrate (120 mg; 0,706 mmol) in distilled water (3 ml) was treated dropwise with aqueous potassium persulphate (122 mg; 0,452 mmol) in distilled water (10 ml) under nitrogen, over a period of 55 min and at 70°C (bath temperature). The resulting solution was stirred for a further 90 min at 70°C, and then poured into water (150 ml) and extracted with dichloromethane. Solvent was stripped from the dried ($MgSO_4$) extract to leave a residue which was chromatographed using ethyl acetate – light petroleum (4:1) as eluent to afford the very unstable *quinone* (**22**) (16 mg; 14%) as an oil; ν_{max} (neat) 3400, 1723, and 1664 cm^{-1}, δ 0,93 (3H, distorted t, *J* 6 Hz, 5′-CH_3), 1,43 [6H, d, *J* 6,5 Hz CH(CH_3)$_2$], 1,20—1,80 (4H, m, 3′- and 4′-H), 2,5 (1H, m 2′-H), 2,86 (3H, d, *J* 5 Hz, NCH_3), 3,83 (3H, s, OCH_3), 4,70 [1H, septet, *J* 6,5 Hz, C*H*(CH_3)$_2$], 6,55 (1H, d, *J* 2,5 Hz, 6-H), 7,05 (1H, d, *J* 2,5 Hz, 8-H), 7,35 (1H, br. s, NH), and 7,90 (1H, s, D_2O exchangeable, OH) (Found: M^+, 389,1816. Calc. for $C_{21}H_{27}NO_6$: *M*, 389,1838).

4,5-Dimethoxy-1,7-di-(2-propyloxy)-3-N,N-dimethylnaphthamide (**23**)

The amide (**19**) (357 mg; 0,989 mmol) in dry tetrahydrofuran (20 mol) was treated with sodium hydride (50% dispersion; 475 mg) and stirred for 15 min. Iodomethane (9 g; 63,34 mmol) was added and stirring was continued for a further 3 h. Thereafter, saturated aqueous ammonium chloride (10 ml) was slowly added and the resulting mixture was extracted with ether (4 × 10 ml). The residue obtained from dried ether extracts was chromatographed using ethyl acetate – light petroleum (3:2) as eluent to afford the *tertiary amide* (**23**) (345 mg; 93%), m.p. 93—94°C (from ethyl acetate – light petroleum); ν_{max} 1615, 1595, and 1585 cm^{-1}; δ 1,41 [12H, d, *J* 6,5 Hz, 2 × CH(CH_3)$_2$], 2,90 and 3,13 [each 3H, s, N(CH_3)$_2$], 3,80 and 3,95 (each 3H, s, OCH_3), 4,70 [2H, septet, *J* 6,5 Hz, 2 × C*H*(CH_3)$_2$], 6,37 (1H, d, *J* 2,5 Hz, 6-H), 6,63 (1H, s, 2-H), and 7,16 (1H, d, *J* 2,5 Hz, 8-H) (Found: C, 67,10; H, 7,60; N, 3,65%; M^+, 375,2017. Calc. for $C_{21}H_{29}NO_5$: C, 67,16; H, 7,73; N, 3,73%; *M*, 375,2045).

5-Methoxy-7-(2-propyloxy)-3-N,N-dimethylcarboxamido-1,4-naphthoquinone (**24**)

The amide (**23**) (330 mg; 0,88 mmol) and silver(II) oxide (436 mg; 3,5 mmol) in dioxane (6 ml) were treated dropwise and with stirring with nitric acid (6M; 3 ml) over a period of 4 min. Work-up as for compound (**20**) followed by chromatography using ethyl acetate as eluent gave the *quinone* (**24**) (40 mg; 14%), m.p. 155—157°C (from acetone – light petroleum); ν_{max} 1635 and 1590 cm^{-1}; δ 1,41 [6H, d, *J* 6,5 Hz, $CH(CH_3)_2$], 2,95 and 3,12 [each 3H, s, $N(CH_3)_2$], 3,96 (3H, s, OCH_3), 4,70 [1H, septet, *J* 6,5 Hz, $CH(CH_3)_2$], 6,73 (1H, d, *J* 2,5 Hz, 6-H), 6,80 (1H, s, 2-H), 7,20 (1H, d, *J* 2,5 Hz, 8-H) (Found: C, 64,35; H, 6,05; N, 4,50. Calc. for $C_{17}H_{19}NO_5$: C, 64,35; H, 6,00; N, 4,42%).

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