

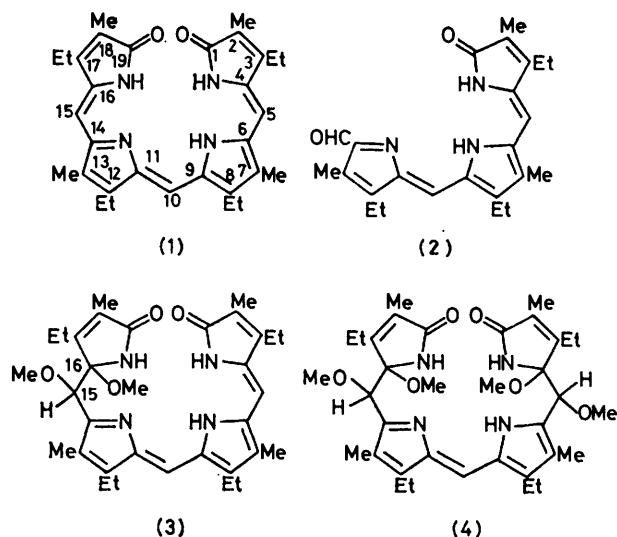
Bile Pigment Studies. Part 5.¹ Some Fragmentation Reactions of Bilindiones (Bilindiones)^{2, 3}

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Anodic oxidation of the model bilindione (1) at platinum electrodes in the presence of methanol gives a good yield of the 15,16-dimethoxybilindione (3). With nickel(II) acetate, this compound gives the chelate (6) which fragments upon treatment with acid to afford the tripyrrinone aldehyde (2) *via* the vinyl ether (8). When the metal-free 15,16-dimethoxybilindione (3) is treated with aqueous acid the same tripyrrinone aldehyde (2) together with the parent bilindione (1) are obtained.

THOUGH a great deal is known about the structural, medicinal, and biological properties of bile pigments,

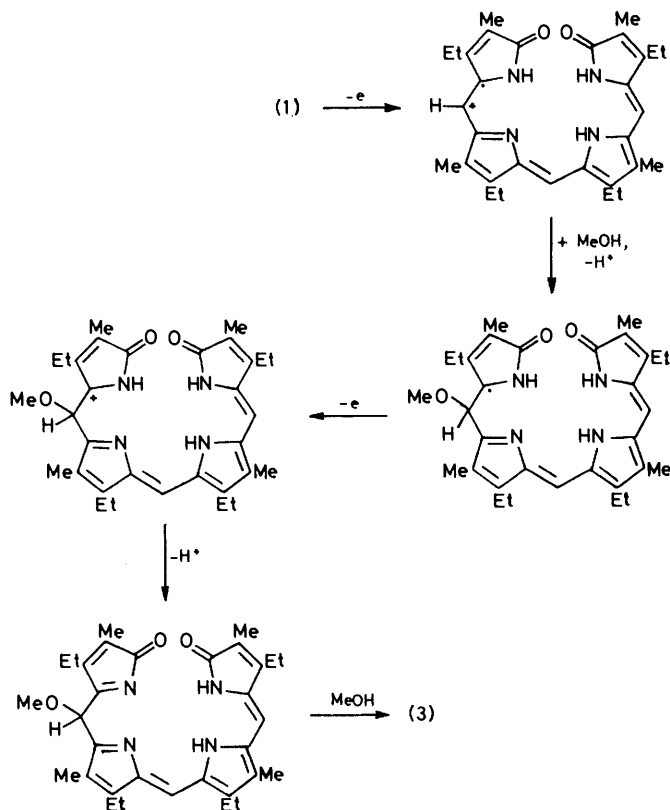
ation with thallium(III) acetate in methanol.¹⁰ We have interpreted¹⁰ these transformations as involving initial formation of the bilindione cation radical (through one-electron oxidation) followed by attack with methanol as a nucleophile on this species or on the dication obtained by abstraction of a second electron. These considerations prompted us to attempt to form compound (3) by anodic oxidation. Cyclic voltammetry[‡] in CH₂Cl₂ containing 0.1M [NBu₄][ClO₄] showed three oxidation waves; the first and second of these (at *ca.* 300 mV and 1.1 V) were clearly reversible, and a preliminary interpretation is that these two waves correspond to cation radical and dication formation. Preparative



relatively little is known about the organic chemistry of these important systems.⁴⁻⁶ The Gmelin reaction, a classical reaction of bile pigments, has been studied only in a qualitative fashion and it is only recently that a 5-nitrobilindione has been identified⁷ as an intermediate in this colour test. Our recent work has centred on controlled oxidation of bilindiones [*e.g.* (1)]^{8,9} using reagents such as lead(IV) and thallium(III) salts,^{10,11} and we have identified and characterized a novel photo-oxidative cleavage to afford the tripyrrinone aldehyde (2).^{10,12} Derivatives of 15,16-dimethoxybilin-1,19-dione (3) are important intermediates in the cleavage reaction; in this paper we describe an efficient electrochemical synthesis of compound (3) and some additional chemistry of this system and metal complexes derived from it.

RESULTS AND DISCUSSION

15,16-Dimethoxybilin-1,19-diones such as (3) have previously been prepared either by treatment of bilindiones [*e.g.* (1)] with bromine in methanol,¹³ or by oxid-



SCHEME 1

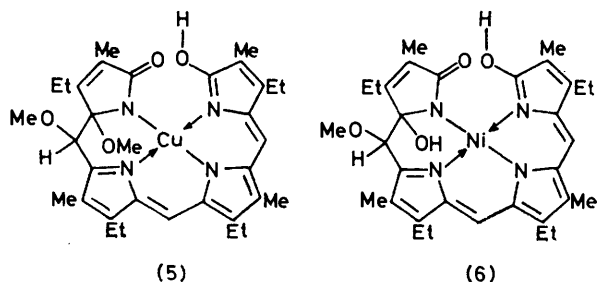
electrolysis of compound (1) (in CH₂Cl₂-MeOH containing 0.05M [NBu₄][ClO₄]) at platinum electrodes in an

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[‡] See ref. 2 for a Figure displaying the cyclic voltammogram. We thank Mr. W. M. Lewis for measurement of the voltammogram.

undivided cell at a potential of 0.7 V (*vs.* the s.c.e.) afforded a 73% yield of the 15,16-dimethoxybilin-1,19-dione (3). Scheme 1 shows a mechanistic proposal for the formation of this compound. At higher potentials and for longer electrolysis times this product was unstable and was further transformed into a product identified spectroscopically (*cf.* ref. 13) as the tetramethoxy-derivative (4); the tripyrrinone aldehyde (2) was also isolated from this experiment.

Treatment of (3) with thallium(III) acetate in methanol afforded¹⁰ the thallium(III) complex which showed two methoxy resonances in its ¹H n.m.r. spectrum (τ 6.71 and 7.04). If the 15,16-dimethoxybilin-1,19-dione (3) was treated instead with copper(II) acetate in methanol then a 52% yield of the paramagnetic copper(II) complex (5) was obtained; evidence for the presence of the two methoxy groups was provided by combustion analysis and by the fact that acid demetallation gave back the 15,16-dimethoxy-compound (3). However, formation of the nickel(II) complex using nickel(II) acetate in methanol gave a diamagnetic product which we believe to be the monohydroxy-monomethoxy-derivative (6) because (a) the ¹H n.m.r. spectrum indicated only one methoxy group (at τ 6.59), (b) the combustion analysis could be correlated with one hydroxy and one methoxy

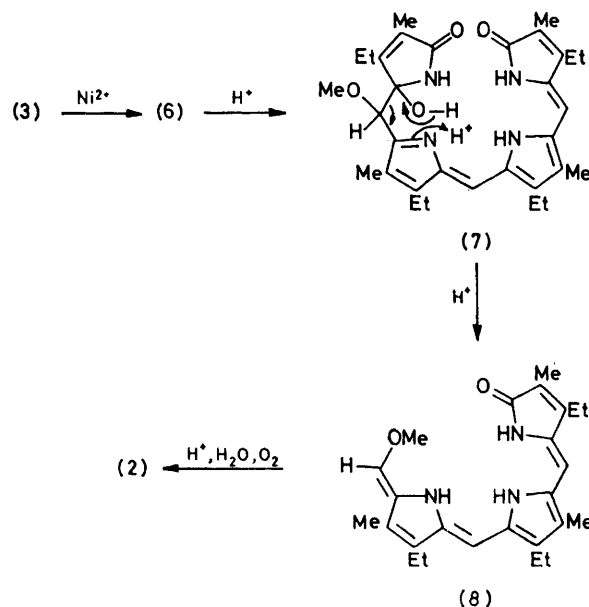


being present, and (c) although complicated, the mass spectra indicated significant fragmentations of methanol from the molecular ion of (5) and water from (6); the high-mass regions did, however, show peaks which could not be assigned to any sensible fragmentation.

In an attempt to obtain the new metal-free ligand (7), the nickel(II) complex was treated with trifluoroacetic acid. Two compounds were isolated; owing to its lability, the most mobile of these on preparative thick-layer chromatography was not characterized by combustion analysis, but n.m.r. and mass spectroscopy showed it to be the vinyl ether (8). The more polar t.l.c. fraction was shown, by comparison with authentic material, to be the tripyrrinone aldehyde (2). Treatment of the vinyl ether (8) with dilute acid in air (or even with unpurified deuteriochloroform in an n.m.r. tube) gave a quantitative yield of the tripyrrinone aldehyde (2). Scheme 2 presents a possible mechanistic route for the formation of (3) *via* (6), (7), and (8).

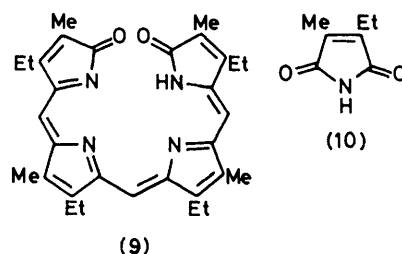
The nickel(II) insertion reaction to give chelate (6) demonstrated lability of the 16-methoxy substituent in this series of compounds. (von Döbeneck has already shown similar lability in a simpler dipyrrolic system.¹³)

Thus, treatment of the 15,16-dimethoxybilin-1,19-dione (3) with aqueous perchloric and acetic acid gave two



SCHEME 2

major products which were readily characterized as the parent bilindione (1) and the tripyrrinone aldehyde (2). We envisage formation of (2) as proceeding through (7) (obtained by protonation of the 16-methoxy group, loss of methanol, and then hydration). Compound (1) could in principle be obtained by similar double elimination of methanol from (3) to give an unstable species such as (9). Reduction would then give (1) and it is noticeable that in the same mixture the tripyrrolic vinyl ether is transformed into (3) by a reaction sequence which requires an oxidation step. Ethylmethylmaleimide (10) was identified¹⁴ as a product in the formation



of the tripyrrinone aldehyde (2) from (6) and (3) as described above.

EXPERIMENTAL

M.p.s were measured on a microscopic hot stage. T.l.c. monitoring was performed using thin layers of silica gel G on glass plates. Preparative thick layer separations were carried out on 20 × 20 cm plates coated (1 mm) with Merck silica gel G. Electronic absorption spectra were measured on a Unicam SP 800 spectrophotometer, using solutions in chloroform unless otherwise stated. Hydrogen-1 n.m.r. spectra were measured (in deuteriochloroform solution

with tetramethylsilane as internal standard) using a Varian XL-100 or Perkin Elmer (220 MHz) R-34 instrument, and mass spectra (direct insertion probe, 70 eV, 50 μ A, source temperature *ca.* 200 °C) using an AEI MS12 spectrometer. Electrochemical oxidations were performed using a Chemical Electronics (Birtley) TR70/2A potentiostat; the working electrode was a platinum mesh cylinder (4 cm long \times 0.75 cm diameter) and the counter-electrode was a standard (EIL) platinum plate (*ca.* 0.5 \times 0.5 cm). Potentials were referenced to a standard (EIL) remote calomel electrode.

Preparation of 3,8,12,17-Tetraethyl-15,16-dimethoxy-2,7,13,18-tetramethyl-15,16-dihydrobilin-1,19(21H,24H)-dione (3).—(a) *By anodic oxidation.* 3,8,12,17-Tetraethyl-2,7,13,18-tetramethylbilin-1,19(21H,24H)dione (1) (100 mg) in methanol (9 ml) and methylene chloride (81 ml) containing tetra-n-butylammonium perchlorate (1 g) was electrolyzed at platinum electrodes at 0.7 V *vs.* the s.c.e. in an undivided cell with stirring (magnetic stirrer bar). The reaction was monitored by spectrophotometry, and on average was completed within 1 h. The mixture was washed with water (10 \times 400 ml), dried (Na_2SO_4), and evaporated to dryness. The product was purified by thick-layer chromatography [elution with methanol–methylene chloride (4 : 96)]; the main (purple) band was the required 15,16-dimethoxybilindione (3) which, after extraction from the silica gel was crystallized from methylene chloride–n-hexane (82 mg, 73%), identical in all respects with an authentic sample.¹⁰ When the bilindione (1) was electrolyzed at 0.9 V (*vs.* the s.c.e.) for >75 min, thick-layer chromatography showed a fast-running red band, identified as the tripyrrinone aldehyde (2), and a yellow band which was removed from the silica gel and crystallized from methylene chloride–n-hexane to give a small quantity of 3,8,12,17-tetraethyl-4,5,15,16-tetramethoxy-2,7,13,18-tetramethyl-4,5,15,16-tetrahydrobilin-1,19(21H,24H)-dione (4), m.p. >300 °C; τ 3.15 (10-H), 5.25 and 5.48 (each 1 H, 5-H and 15-H); 6.70 (3 H), 6.81 (6 H), and 6.95 (3 H) (4 OMe); 7.51 and 7.63 (each 4 H, q, CH_2CH_3); 7.95, 7.99, 8.03, 8.04 (each 3 H, 4 Me); and 8.91 (12 H, m, CH_2CH_3); λ_{max} 450 nm (ϵ 70 500); in CHCl_3 + 1% trifluoroacetic acid, 500 nm (ϵ 150 000); *m/e* 622 (1%), 469 (11), 468 (10), 406 (10), and 315 (100). Careful analytical thin-layer chromatography indicated the presence of two isomers; attempts to obtain a preparative separation were unsuccessful.

(b) *By oxidation with thallium(III) acetate.*—Bilindione (1) (100 mg) in dry methanol (25 ml) was treated with thallium(III) acetate (237 mg; 3 equiv.) in methanol (8 ml) and the mixture was left stirring overnight before being worked-up by addition of water and methylene chloride, drying of the organic phase (Na_2SO_4), and evaporation to dryness. The residue was chromatographed on preparative thick-layer plates [elution with methanol–methylene chloride (4 : 96)] to give two major fractions. The most polar of these was the 15,16-dimethoxybilindione (3) which was crystallized from methylene chloride–n-hexane to give 35 mg (32%) of purple crystals identical with material described in (a). The least polar fraction gave a compound, red in colour, which was chromatographically more mobile than the tripyrrinone aldehyde. Extraction from the silica gel and crystallization from methylene chloride–methanol gave 15 mg (20%) of 3,8,12-triethyl-14-methoxy-2,7,13-trimethyl-

1(15H)-tripyrrinone, as bright red needles, m.p. 155–156 °C (Found: C, 73.0; H, 7.9; N, 11.0. $\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_2$ requires: C, 73.2; H, 7.9; N, 10.7%); τ –3.40 and –2.95 (each 1 H, br, 2 \times NH), 3.61 and 4.04 (each 1 H, methine H), 5.81 (3 H, OMe), 7.42, 7.49, and 7.54 (each 2 H, q, CH_2CH_3), 7.90, 8.10, and 8.12 (each 3 H, Me), and 8.75, 8.81, and 8.85 (each 3 H, t, CH_2CH_3); *m/e* 393 (100%), 378 (57), 348 (11), and 334 (14); λ_{max} 521 (ϵ 32 300), 498 (35 000), and 323 nm (48 500); λ_{max} in trifluoroacetic acid, 575 (ϵ 35 000), 534 (51 100), and 327 nm (50 000); ν_{max} 1 695 cm^{-1} (KBr).

Phenylhydrazone of the Tripyrrinone Aldehyde (2).—The tripyrrinone aldehyde (2) (25 mg) in methylene chloride (10 ml) was treated with a solution of 2,4-dinitrophenylhydrazine [10 ml of a 2% solution in ethanol–1M hydrochloric acid (10:1)]. After stirring for 1 h the colour changed from red to green and the mixture was poured into water (100 ml), washed with sodium hydrogencarbonate solution, dried (Na_2SO_4), and evaporated to dryness to give a green highly insoluble residue which was precipitated twice from methylene chloride–n-hexane to give an amorphous powder (15 mg; 40%), m.p. 290 °C (decomp.) (Found: C, 61.6; H, 5.9; N, 16.9. $\text{C}_{30}\text{H}_{35}\text{N}_7\text{O}_6$ requires: C, 61.1; H, 5.9; N, 16.6%); λ_{max} in CHCl_3 – $\text{CF}_3\text{CO}_2\text{H}$ (1 : 1), 580 nm (ϵ 13 300); *m/e* 571 (10%), 521 (2), 457 (15), 391 (53), 378 (50), 285.5 (6), 211 (100), and 192 (60).

3,8,12,17-Tetraethyl-15,16-dimethoxy-2,7,13,18-tetramethyl-15,16-dihydrobilin-1,19(21H,24H)-dione–Copper(II) Complex (5).—The 15,16-dimethoxybilindione (3) (20 mg) in methylene chloride (15 ml) was treated with copper(II) acetate (10 mg) in methanol (4 ml). The mixture was heated on a water bath for 40 min and the solvent was then evaporated off to give a residue which was chromatographed on thick-layer silica gel plates [elution with methanol–methylene chloride (4 : 96)]. The blue major band was removed from the silica gel and crystallized from methylene chloride–methanol to give the copper(II) complex (12 mg; 52%), m.p. 262–263 °C (Found: C, 63.3; H, 6.6; N, 9.2. $\text{C}_{32}\text{H}_{40}\text{CuN}_4\text{O}_4$ requires: C, 63.2; H, 6.6; N, 9.2%); *m/e* (^{63}Cu), 622 (20%), 604 (100), 589 (50), 528 (70), and 302 (9); λ_{max} 620 (ϵ 77 900) and 345 nm (80 000).

3,8,12,17-Tetraethyl-16-hydroxy-15-methoxy-2,7,13,18-tetramethyl-15,16-dihydrobilin-1,19(21H,24H)-dione–Nickel(II) Complex (6).—The 15,16-dimethoxybilindione (3) (100 mg) in methylene chloride (30 ml) was treated with nickel(II) acetate (400 mg) in methanol (12 ml) and then left to stir at room temperature for 90 min. Spectrophotometry showed no starting material to be present so the mixture was poured into water (200 ml), extracted with methylene chloride (100 ml), dried (Na_2SO_4), and then evaporated to dryness. The residue was chromatographed on silica gel thick-layer plates [elution with methanol–methylene chloride (1 : 20)] and extraction of the silica gel gave a residue which was crystallized from methylene chloride–n-hexane to give the nickel(II) complex (78 mg; 71%), m.p. >300 °C (Found: C, 63.8; H, 6.6; N, 9.5. $\text{C}_{32}\text{H}_{40}\text{N}_4\text{NiO}_4$ requires: C, 63.9; H, 6.7; N, 9.3%); τ 3.19 and 4.01 (5- and 10-H), 6.10 (15-H), 6.59 (3 H, OMe), 7.41, 7.46, 7.57, and 7.60 (8 H, each q, CH_2CH_3), 7.98, 8.09, 8.22, and 8.24 (each 3 H, Me), and 8.67 (3 H), 8.70 (3 H), and 8.72 (6 H) (CH_2CH_3); *m/e* (^{58}Ni) 617 (42%), 585 (47), 553 (100), and 462 (53); λ_{max} 638 (ϵ 50 500) and 344 nm (53 500).

Demetallation of the Nickel(II) Complex (6).—The fore-

* A more efficient experiment is described in ref. 3.

going nickel(II) complex (25 mg) in trifluoroacetic acid (5 ml) was stirred at room temperature for 30 min before being poured into water (50 ml) and extracted with methylene chloride. The organic extracts were washed until neutral with sodium hydrogencarbonate solution, dried (Na_2SO_4), and then evaporated to dryness to give a residue which was chromatographed on thick-layer plates. The most mobile fraction, purple in colour, was very labile and therefore not fully characterized. It was identified as the tripyrrolic vinyl ether (8): mass spectrum, m/e 407 (53%), 391 (100), 374 (95), 361 (71), 349 (23), 332 (47), and 203.5 (5); n.m.r. spectrum (in rigorously dried and purified CDCl_3), at τ 3.21 and 3.31 (2 methine-H), 4.01 (vinylic H), 7.41 (6 H, m, CH_2CH_3), 7.60 (3 H, OMe), 7.79, 7.91, and 8.02 (3 Me), and 8.76 (9 H, m, CH_2CH_3). Brief treatment in air with aqueous hydrochloric acid (1 drop) in methylene chloride gave a quantitative yield of the tripyrrolic aldehyde (2). The most polar compound on the thick-layer plate was extracted and shown to be the tripyrrolic aldehyde (2). When the reaction was carried out with no attempt to isolate the vinyl ether (8), an overall yield of 78% of the tripyrrolic aldehyde was obtained.

Treatment of the 15,16-Dimethoxybilindione (3) with Aqueous Acid.—The 15,16-dimethoxybilindione (3) (30 mg) was stirred in perchloric acid–acetic acid (20 ml, 1 : 1) during 30 min. Water (50 ml) was then added and the mixture was stirred in an ice-bath for 2 h before filtration of the precipitate. After drying, the precipitate was chromatographed on silica gel thick-layer plates [elution with methanol–methylene chloride (4 : 96)]. The major, fast moving zone, red in colour, was extracted from the silica gel; crystallization from methylene chloride–n-hexane yielded 10 mg (49%) of the tripyrrolic aldehyde

(2), identical with an authentic sample. A more polar band, blue in colour, was shown to contain the bilindione (1) (10 mg; 40%). A very polar yellow band contained a small amount of material which remains unidentified.

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