Tetrahedron Letters No. 42, pp 3837 - 3840, 1976. Pergamon Press. Printed in Great Britain.

CONTROLLED OXIDATION OF BILE PIGMENTS

Fahimeh Eivazi, Mervyn F. Hudson, and Kevin M. Smith*
The Robert Robinson Laboratories, University of Liverpool,
P.O. Box 147, Liverpool L69 3BX

(Received in UK 23 July 1976; accepted for publication 6 September 1976)

We have shown[1] that treatment of bile pigments with thallium(III) salts results in the formation of compounds possessing the so-called[2] "bilipurpurin" chromophore. Furthermore, using controlled oxidation with thallium(III) or lead (IV) reagents it is possible to imitate the series of colour changes characteristic of the classical Gmelin reaction, the first reaction of bile pigments to be discovered.[3] Trivial names (*e.g.* bilipurpurin, chrysin, choletelin, etc.) have been attached to the chromophores thought to be responsible for the colours in the Gmelin reaction, but little structural work aimed at identification of the actual products has been carried out. In this Letter we report initial studies in this direction, and show that it is possible to detach one terminal ring from bilitrienes to give fully characterised tripyrrolic compounds.

Aetiobiliverdin-IVγ (1)[4], a readily available symmetrically substituted bilitriene was used as the substrate. Treatment with 1 equiv of thallium (III) acetate in methanol gave rapidly a green solution (Figure) of the thallium(III) complex (2)[5] (ν_{max} 1580 cm^{-1}, OCOMe). When stirred in air[6] in the absence of light, a blue solution (Figure) was next formed; the blue compound was labile and difficult to handle, but on the basis of its demetallation [to give (4)[7]] and its ready re-metallation, we assign structure (3) to it. The zinc(II) complex (5) prepared from compound (4) possessed an electronic absorption spectrum similar to that of compound (3).

The thallium(III) complex (3) was photolabile;[8] exposure of a solution of (3) to light[9] gave ethylmethylmaleimide (identified by tlc[10]), the de-metallated bilipurpurin (4), and the tripyrrole aldehyde (6) [mp 181-3°;

τ, 0.14 (CHO), 3.33, 4.13 (methine H), see Figure for visible spectrum.] When the reaction between (1) and thallium(III) acetate was carried out in acetic acid only two major products were obtained, namely the tripyrrole aldehyde (6) and the tetrapyrrole (7) [mp 187-8°; τ, 3.27, 4.12 (methine H).]

Several methods for degradation of bile pigments have been described (for review see Ref. 11), but the present work describes the first example of controlled removal of one ring from a bilitriene; work on optimisation of this procedure for structural work is in progress.

Since the thallium(III) atom is retained in the formation of (3) from (2) it appears that aerial oxidation is responsible for this transformation.[6] We envisage initial formation of the cation radical[12] (8), followed by nucleophilic attack by methanol[13] [to give (9)] before further one electron abstraction and reaction with methanol to give (3).

The photochemical lability of thallium(III) compounds is well understood; thus for the transformation of (3) into (6) we anticipate

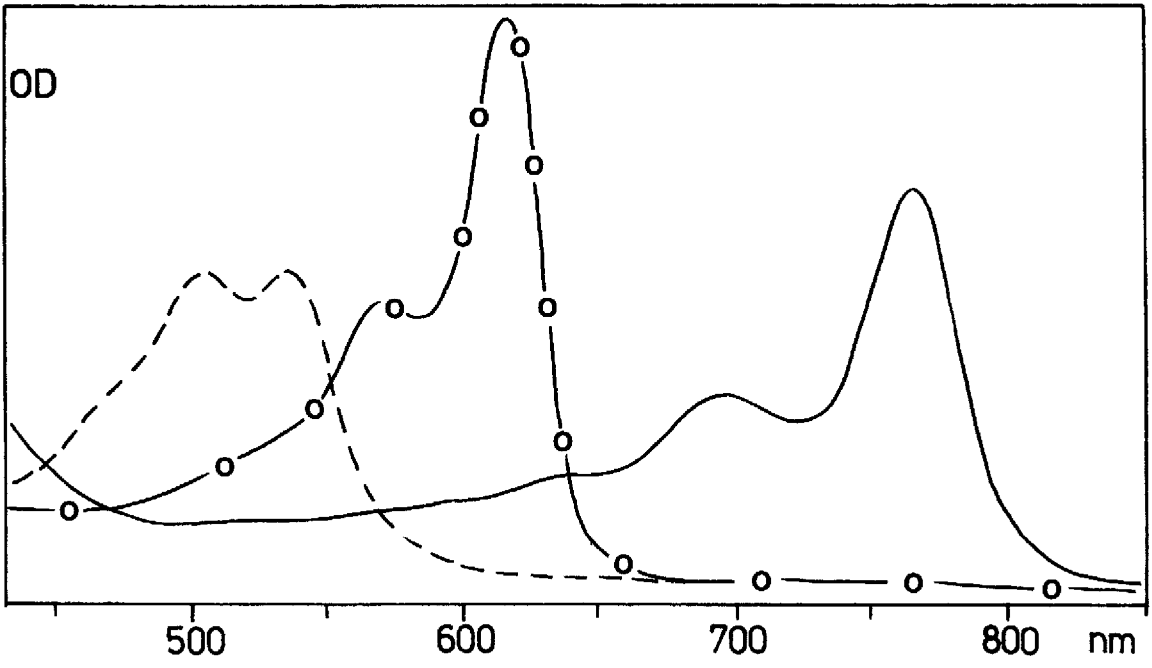
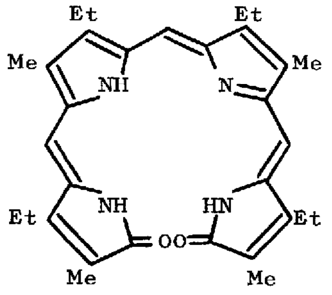
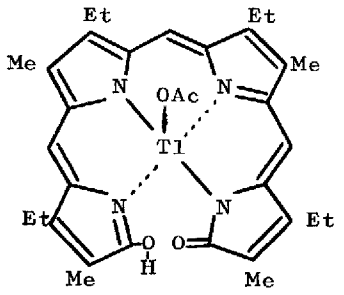


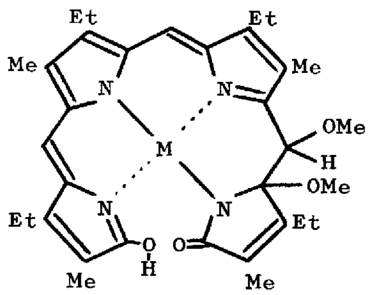
FIGURE Visible absorption spectra (450-850 nm only) in CH_2Cl_2 of: —— Compound (2); –o—o—o– Compound (3); – – – – Compound (6).



(1)



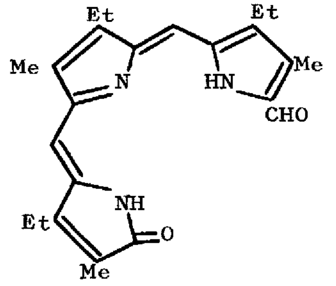
(2)



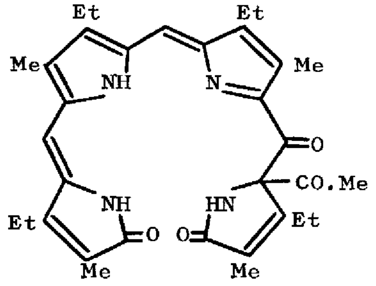
(3) M = Tl-OAc

(4) M = 2H

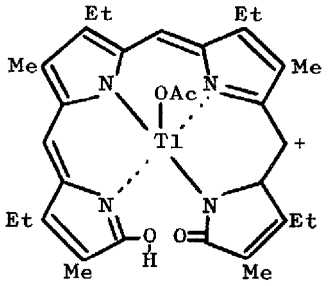
(5) M = Zn



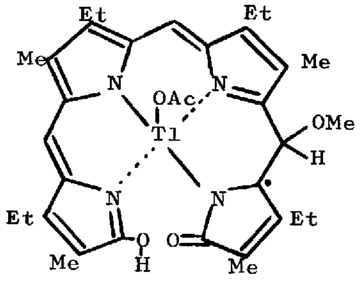
(6)



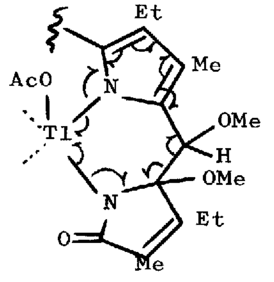
(7)



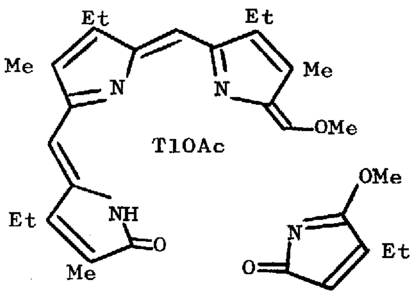
(8)



(9)



(10)



(11) (12)

fragmentation, as shown in (10), to give (11) and (12), and eventually ethylmethylmaleimide and the tripyrrole aldehyde (6).

Acknowledgement: We thank Azarabadegan University (Tabriz, Iran) for financially supported leave to F.E., and the S.R.C. for a fellowship (to M.F.H.).

References and Notes

1 J.A.S. Cavaleiro and K.M. Smith, J.C.S. Perkin I, 2149 (1973).

2 (a) R. Lemberg and J.W. Legge, "Haematin Compounds and Bile Pigments", Interscience, New York, 1949, p. 130; (b) T.K. With, "Bile Pigments", Academic Press, New York, 1968, p. 56.

3 F. Tiedemann and L. Gmelin, "Die Verdauung nach Versuchen", 1st Edn., Karl Groos, Heidelberg and Leipzig, 1826.

4 K.M. Smith, J.C.S. Perkin I, 1471 (1972).

5 This compound was only stable in solution in the absence of air and nucleophilic solvents; it was prepared for characterisation by treatment of (1) in CH_2Cl_2 with thallium(III) acetate in CH_3CN, followed by dilution of the mixture by slow addition of n-hexane until crystallisation occurred.

6 Exclusion of air considerably retarded the reaction whereas passage of a stream of air through the mixture increased the rate of reaction.

7 Dimethoxybilipurpurins of this type are known; see Ref. 2a, p. 110.

8 The photochemical lability of thallium(III) carboxylates has been studied, J.K. Kochi and T.W. Bethea III, J. Org. Chem., **33**, 75 (1968).

9 The free base (4) and the zinc(II), copper(II) and nickel(II) complexes from it were stable under these conditions.

10 W. Rüdiger, Z. Physiol. Chem., **350**, 1291 (1969).

11 M.F. Hudson and K.M. Smith, Chem. Soc. Reviews, **4**, 363 (1975).

12 Cation radicals of bile pigment derivatives are readily formed; for example see J. Subramanian, J.-H. Fuhrhop, A. Salek, and A. Gossauer, J. Magn. Resonance, **15**, 19 (1974).

13 It is possible that the second electron is abstracted before attack by the nucleophile; in mechanistic problems of this type it is fundamentally difficult the ascertain the precise order of the steps involved.