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Synthesis of γ-Oxyprotoporphyrin IX and Pterobiline (Biliverdin IXγ)

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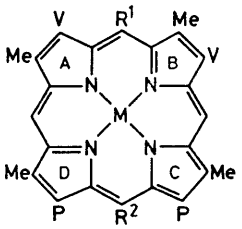
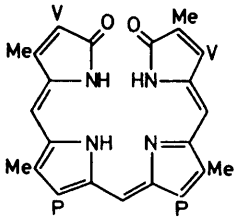
Summary The γ-*meso*-hydroxy-derivative of protoporphyrin IX has been synthesised by condensation of a bis(formylpyrrolyl) ketone and a dipyrrolylmethane; the iron complex underwent oxidative ring-opening to give biliverdin IXγ (pterobiline), the blue-green butterfly pigment, thus providing a model for its biosynthesis.

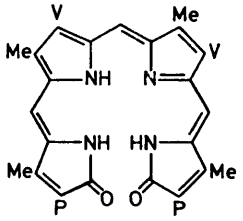
THE vast majority of naturally occurring bile pigments, whether of animal or plant origin, are derived from haem (**1a**) *via* α-*meso*-oxyhaem (**2a**), followed by oxidative ring-opening;[1] the initial product of ring-opening, biliverdin IXα (**3a**) may then undergo enzymic reduction to form bilirubin and other mammalian and plant bile pigments.[2] Certain species of lepidoptera, however, produce a series of blue-green pigments[3] related to biliverdin IXγ (**5a**) ('pterobiline') and it would clearly be of interest to know whether they are also formed from haem (**1a**) by a similar process involving enzymic oxidation at the γ-positions rather than the α-position. We have, therefore, synthesised the γ-oxygenated derivative (**4a**) of protoporphyrin IX by the method illustrated in the accompanying Scheme and have studied the ring opening of the iron complex.



(1) $R^1 = R^2 = H$, $M = Fe^{II}$
(2) $R^1 = OH$, $R^2 = H$, $M = Fe^{II}$
(4) $R^1 = H$, $R^2 = OH$, $M = H_2$



(3)

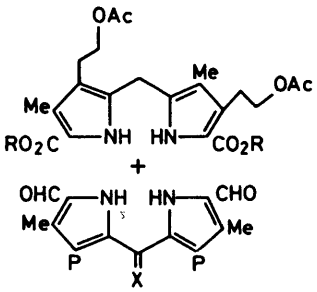


(5)

a; P = $CH_2CH_2CO_2H$, V = $CH{=}CH_2$
b; P = $CH_2CH_2CO_2Me$, V = $CH{=}CH_2$

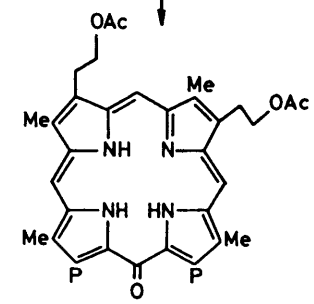
Retro-synthetic analysis led us to the conclusion that the most efficient route would be a MacDonald-type synthesis[4-6] from two dipyrrolyl units, rather than an open-chain tetrapyrrole, owing to the symmetrical nature of the substitution pattern in rings C and D of the γ-oxyprotoporphyrin IX dimethyl ester (**4b**).

In order to introduce the *meso*-oxygen function we synthesised the symmetrical bis(formylpyrrolyl) ketone (**7b**) by sulphuryl chloride oxidation[5] of the related dipyrrolylmethane (**7a**). The unsymmetrical dipyrrolylmethane (**6a**), required for rings A and B of the oxy-porphyrin, was synthesised from individual pyrrole units, which had been prepared by variations of the standard methods. Condensation of the bis(formylpyrrolyl) ketone (**7b**) with the

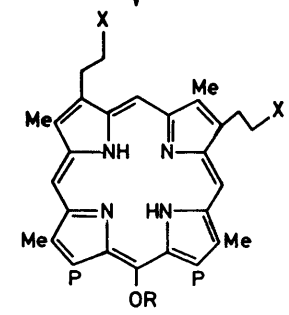


(6)
a; R = CH_2Ph
b; R = H

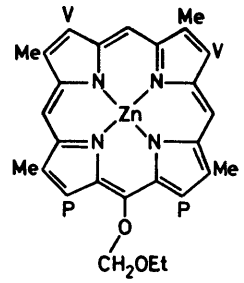
(7)
a; X = H_2
b; X = O



(8)



(9)
a; R = COPh, X = OAc
b; R = COPh, X = OH
c; R = COPh, X = Cl
d; R = CH_2OEt, X = Cl



(10)
↓
(4b)
↓
(5b)

P = $CH_2CH_2CO_2Me$
V = $CH{=}CH_2$

SCHEME

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dipyrrolylmethanedicarboxylic acid (**6b**) in trifluoroacetic acid at 20 °C for 2 h gave the blue-green oxophlorin (**8**) in 48% yield, and this was isolated as the *O*-benzoyl derivative (**9a**) after treatment with benzoyl chloride in pyridine. (In earlier studies with oxophlorins we had converted them into the *O*-acetyl derivatives, but the *O*-benzoyl derivative was chosen in this case because of its greater stability to acid and base hydrolysis.) Acid-catalysed methanolysis of the side-chain acetoxyethyl groups gave the bis(hydroxyethyl)-porphyrin (**9b**) which was subsequently converted into the bis(chloroethyl) analogue (**9c**), either with thionyl chloride in dimethylformamide or with mesyl chloride in pyridine.

Many attempts were made to dehydrochlorinate the zinc complex of this bis(chloroethyl)-porphyrin using a variety of basic catalysts, but either no reaction occurred or concomitant cleavage of the *O*-benzoyl group took place, and the resultant oxophlorin anion decomposed under the conditions of the reaction. However, brief treatment of the zinc benzoyloxyporphyrin with methanolic potassium hydroxide followed by reaction with chloromethyl ethyl ether in the presence of the non-nucleophilic base 1,8-diaminonaphthalene gave the ethoxymethoxy-porphyrin (**9d**) in 85% yield. The zinc complex of the latter was dehydrochlorinated with potassium t-butoxide in t-butanol and the resultant zinc ethoxymethoxy-porphyrin (**10**) was deprotected and demetallated with methanolic boron trifluoride to give the unstable blue-green γ-oxyprotoporphyrin IX dimethyl ester (**4b**).

The latter was converted into its iron complex and oxidised by air in pyridine solution; the intermediate verdohaemochrome was hydrolysed by alkali and re-esterified with methanolic sulphuric acid to give the biliverdin IXγ dimethyl ester (**5b**) in 20% overall yield from the oxy-porphyrin. Small amounts of other blue pigments were also formed and separated chromatographically from the major product. These were presumably similar in structure with the other butterfly pigments which may have been formed by intramolecular cyclisation onto the vinyl groups.[7]

These studies provide an *in vitro* model for the formation of pterobiline and its analogues *in vivo*, and biosynthetic experiments are now in progress.

We thank the S.R.C. for their generous support of this work.

(*Received*, 22*nd April* 1981; *Com.* 479.)

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