Opp-Dibenzoporphyrins from Benzopyrromethene Derivatives

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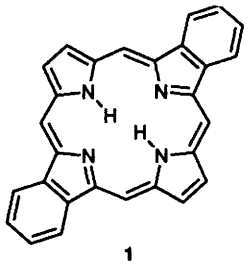
Condensation of 1-formyl-3-haloisoindoles with α-free pyrroles in the presence of hydrogen bromide gives the corresponding benzopyrromethene hydrobromides: heating α-halo-α'-methylbenzopyrromethene hydrobromides in *o*-dichlorobenzene in air provides an economical synthesis of the *opp*-dibenzoporphyrin system in acceptable yields.

Although the tetrabenzoporphyrins have attracted some attention as analogues of the phthalocyanines, the lower benzoporphyrins have been relatively little studied. Such compounds have been encountered in sedimentary deposits and in crude oil,[1,2] and, since they have strong absorption in the red region of the spectrum, they provide chromophores for potential photosensitisers for the photodynamic therapy (PDT) of tumours.[3] The application of 1-formyl-3-haloisoindole building blocks in the synthesis of benzoporphyrins is illustrated here by a novel synthesis of the *opp*-dibenzoporphyrin system **1**.

In studies related to organic geochemical aspects, this type of system has been obtained[4] from the preformed zinc porphyrin (with β-acetic acid ester and β-propionic acid ester substituents suitably arranged) by Dieckmann condensation followed by appropriate modifying steps, as indicated in Scheme 1. In expert hands the yield of this multistage procedure was about 10% from the preformed porphyrin,[4] which was itself prepared by the MacDonald synthesis.

In our approach, the benzo ring is introduced earlier as the isoindole synthon **2**. This is prepared by a double Vilsmeier reaction from phthalimidine **3** (isoindolinone).[5] Condensation of the formylisoindole **2** (X = Cl, Br) with a α-free pyrrole in the presence of hydrogen bromide gives the benzopyrromethene hydrobromide **4** (Scheme 2).

The benzopyrromethene hydrobromides prepared in this way are shown in Table 1. As is usual with pyrromethene salts, attempts to purify by crystallisation considerably reduces yields. Structural assignment rests on elemental analysis, ^1H and ^{13}C NMR spectroscopy and mass spectrometry. In the EI-MS the free base appears as the base peak. The electronic spectra are dominated by an intense rather sharp absorption band at about 540 nm (*e.g.* Fig. 1).



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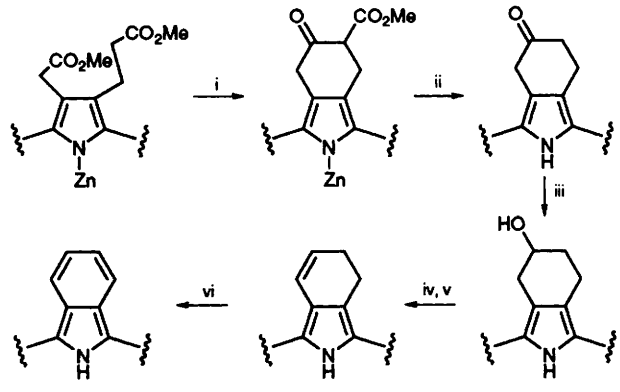
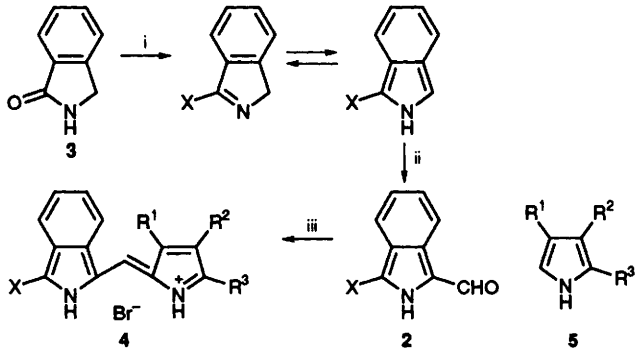
The application of such benzopyrromethene salts in the synthesis of benzoporphyrins is illustrated by the synthesis of the known[4] *opp*-dibenzoporphyrin **6** from the α-halo-α'-methyl benzopyrromethene hydrobromide. Thus heating the benzopyrromethene hydrobromide **4c** (from kryptopyrrole) in *o*-dichlorobenzene (196 °C, 3 h, monitored by VIS spectro-



Scheme 1 Elaboration of benzoporphyrin systems *via* Dieckmann synthesis. *Reagents and conditions*: i, $NaOCMe_2Et$, PhH; ii, HCl (aq); iii, $NaBH_4$; iv, $MeSO_2Cl$; v, NaOH (aq), vi, DDQ.



Scheme 2 Synthesis of benzopyrromethene hydrobromides (X = Cl, Br). *Reagents and conditions*: i, POX_3; ii, POX_3–DMF, then NaOH–EtOH (aq); iii, α-free pyrrole **5**, HBr.

Table 1 Benzopyrromethene hydrobromide synthesis

Isoindole component **2**	Pyrrole component **5**	Benzopyrromethene salt **4**	Yield (%)[a]
X = Cl	$R^1 = R^3 = Me, R^2 = H$	$R^1 = R^3 = Me, R^2 = H$ (**a**)	75
X = Cl	$R^1 = Et, R^2 = R^3 = Me$	$R^1 = Et, R^2 = R^3 = Me$ (**b**)	25
X = Cl	$R^1 = R^3 = Me, R^2 = Et$	$R^1 = R^3 = Me, R^2 = Et$ (**c**)	22
X = Cl	$R^1 = R^2 = Et, R^3 = H$	$R^1 = R^2 = Et, R^3 = H$ (**d**)	22
X = Br	$R^1 = R^2 = Me, R^3 = H$	$R^1 = R^2 = Me, R^3 = H$ (**e**)	25
X = Br	$R^1 = R^2 = Et, R^3 = H$	$R^1 = R^2 = Et, R^3 = H$ (**f**)	31
X = Br	$R^1 = R^3 = Me, R^2 = Et$	$R^1 = R^3 = Me, R^2 = Et$ (**g**)	50
X = Br	$R^1 = R^3 = Me, R^2 = CO_2Et$	$R^1 = R^3 = Me, R^2 = CO_2Et$ (**h**)	11
X = Br	$R^1 = R^2 = R^3 = Me$[b]	$R^1 = R^2 = R^3 = Me$ (**i**)	45

[a] Yields not optimised. [b] As 3,4,5-trimethylpyrrole-2-carboxylic acid.

scopy) in air gave **6a** in 31% yield. Analogously, with **4b** (from haemopyrrole) as precursor, this *opp*-dibenzoporphyrin **6a** was obtained in 54% yield.

Self-condensation of **4a** gave the *opp*-dibenzoporphyrin **6b**, but in low yield (4%), possibly because the free β-position offers an alternative reaction site. The insolubility of the highly symmetrical compound **6c** (from **4i**) caused difficulties in its purification. The electronic spectrum in *o*-dichlorobenzene is shown in Fig. 2. Typically the lowest energy band has λ_{max} *ca.* 650 nm with a high molar extinction (ε 25000) dm^3 mol^{-1} cm^{-1}. Because of the enhanced penetration of red light (as opposed to the blue end of the visible) in tissue,

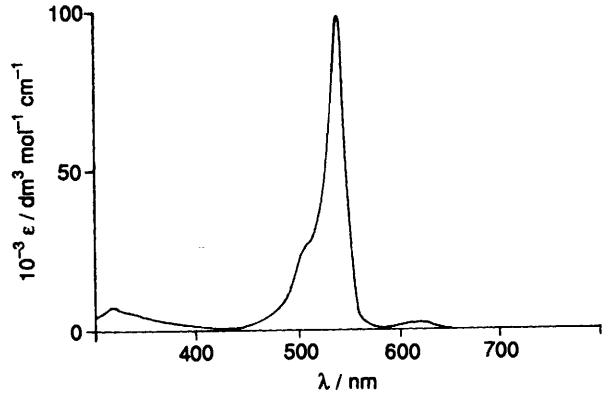
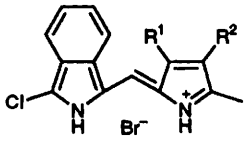


Fig. 1 Electronic spectrum of benzopyrromethene hydrobromide **4c** in chloroform



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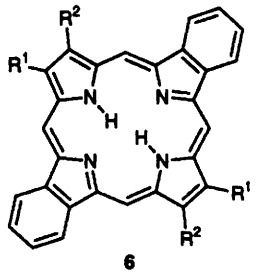
b; R^1 = Me, R^2 = Et
c; R^1 = Et, R^2 = Me



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a; R^1 = Me, R^2 = Et
b; R^1 = Me, R^2 = H
c; R^1 = R^2 = Me

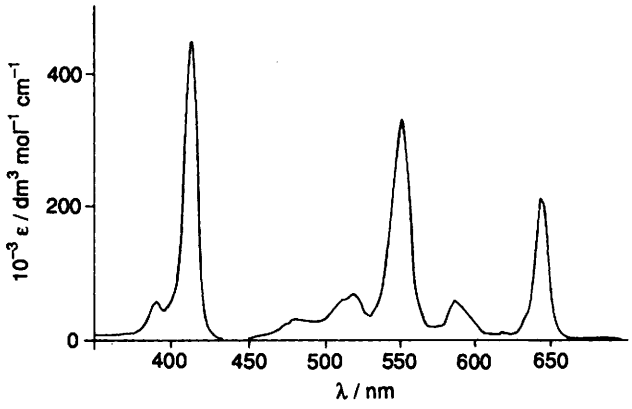

Fig. 2 Electronic spectrum of 2,3,12,13-tetramethyl *opp*-dibenzoporphyrin **6c** in *o*-dichlorobenzene. For the 450–650 nm region the molar extinction scale is reduced to one tenth of that shown.

compounds absorbing strongly in the red are currently attracting attention as photosensitisers for PDT: the *opp*-dibenzoporphyrin system appears to provide a potentially useful chromophore for this purpose.

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References

1 E. W. Baker, T. F. Yen, J. P. Dickie, R. E. Rhodes and L. F. Clarke, *J. Am. Chem. Soc.*, 1967, **89**, 3631.
2 S. Kaur, M. I. Chicarelli and J. R. Maxwell, *J. Am. Chem. Soc.*, 1986, **108**, 1347.
3 R. Bonnett and M. C. Berenbaum, in *Photosensitising Compounds: Their Chemistry, Biology and Clinical Use*, Ciba Foundation Symposium No. 146, Wiley, Chichester, 1989, p. 40.
4 P. S. Clezy and A. H. Mirza, *Aust. J. Chem.*, 1982, **35**, 197.
5 H. von Dobeneck, H. Reinhard, H. Deubel and D. Wolkenstein, *Chem. Ber.*, 1969, **102**, 1357.