Porphyrin β-Keto-esters and their Cyclisation to Phaeoporphyrins

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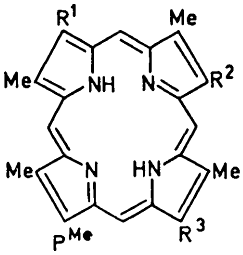
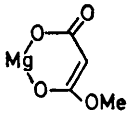
Summary Treatment of porphyrin carboximidazolides with the magnesium complex of methyl hydrogen malonate affords high yields of the corresponding β-keto-esters which are cyclised to phaeoporphyrins when treated with two equivalents of thallium trifluoroacetate followed by photolysis.

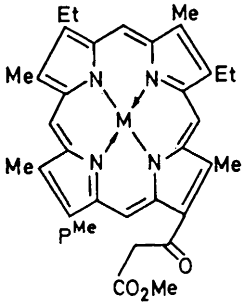
Labelling experiments in a chloroplast system have shown that the carbocyclic ring of chlorophylls *a* and *b* is formed by cyclisation of a magnesium porphyrin β-keto-ester.[1] An analogous non-enzymatic transformation of porphyrin β-keto-esters into phaeoporphyrins, [*e.g.* (**4**)], has potential value as a stage in the total synthesis of chlorophyll derivatives following a biogenetic pattern. The already reported[2] treatment of (**3b**) with iodine and sodium carbonate in methanol was a step in this direction, but the yield was only 7% and a superfluous, irremovable 10-methoxy-substituent was attached to the carbocyclic ring. We now describe efficient means of achieving the β-keto-ester cyclisation.



(1)



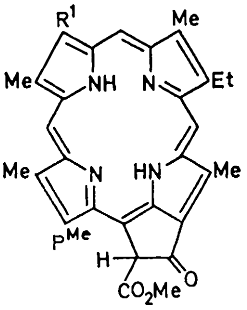
(2)



(3)

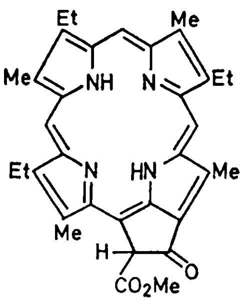
a, $R^1=R^2=Et$; $R^3=CO_2H$
b, $R^1=R^2=Et$; $R^3=\overline{CON{\cdot}CH{:}CH{\cdot}N{:}CH}$
c, $R^1=R^2=Et$; $R^3=CO{\cdot}CH_2{\cdot}CO_2Me$
d, $R^1=V$; $R^2=Et$; $R^3=CO{\cdot}CH_2{\cdot}CO_2Me$
e, $R^1=R^2=V$; $R^3=CO{\cdot}CH_2{\cdot}CO_2Me$
$P^{Me}=CH_2{\cdot}CH_2{\cdot}CO_2Me$ $V=CH{=}CH_2$

a, M = Tl—OCOCF$_3$
b, M = Mg
c, M = Zn



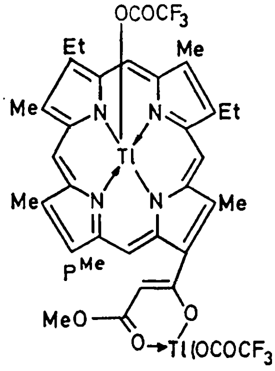
(4)

a, $R^1=Et$
b, $R^1=V$

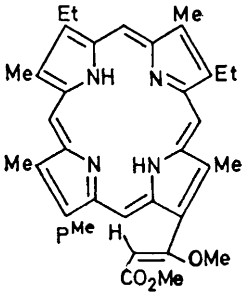


(5)

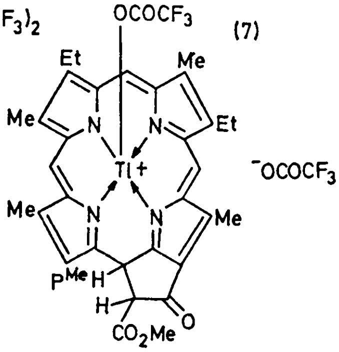
Preparation of the requisite β-keto-esters was improved by employing the elegant method of Bram and Vilkas.[3] Thus, treatment of rhodoporphyrin-XV monomethyl ester (**1a**)[2] with carbonyl di-imidazole gave a high yield of the imidazolide (**1b**),† which reacted smoothly with the magnesium complex (**2**) of methyl hydrogen malonate. The β-keto-ester (**1c**),[2] m.p. 292—294°, was obtained in 80% yield after acidic work-up. In the biologically significant series of vinyl porphyrins, similar yields were obtained of (**1d**),[4] m.p. 250—254° (70%), and (**1e**),[4] m.p. 180—185° (decomp.) (71%); only a low yield of the latter had been obtained from the acid chloride and t-butyl methyl sodiomalonate followed by treatment with trifluoroacetic acid.[4] Like other porphyrin β-keto-esters, these compounds were considerably enolised in deuteriochloroform and trifluoroacetic acid solutions (n.m.r. spectra).



(6)



(7)



(8)

Treatment of the β-keto-esters [*e.g.* (**1c**)] with one equivalent of thallium trifluoroacetate in tetrahydrofuran and methylene chloride gave the corresponding thallium chelate‡ (**3a**)[5] which was apparently stable, even in the light,

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† New compound which gave a satisfactory elemental analysis and visible, n.m.r., and mass spectra compatible with the structure shown.

‡ The nature of the axial ligands in this chelate was not determined.

but was not isolated; a further equivalent of thallium trifluoroacetate produced a compound, which had a characteristic metalloporphyrin visible absorption spectrum (Figure) broadly similar to that of the original chelate (**3a**) and which was stable for many hours when kept in the dark. However, exposure of the reaction mixture to daylight or a quartz/iodine lamp§ for 10 min produced a profound change in the visible absorption spectrum (Figure) due to the production of the thallium chelate of the phaeoporphyrin (**4a**).¶ The thallium was removed by brief treatment of the mixture with sulphur dioxide and acid and phaeoporphyrin-a_5 dimethyl ester (**4a**),†† m.p. 270—272° (lit.,[6] 273°) was obtained in 69% yield from the β-keto-ester (**1c**). Repetition with the 2-vinyl keto-ester (**1d**) gave 2-vinylphaeoporphyrin-a_5 dimethyl ester (**4b**),†† m.p. 288–290° (lit.,[7] 288—292°) in 37% yield.** The synthetic sequence was further exemplified by the preparation of (**5**)†, which showed no m.p. below 300°, in high overall yield.

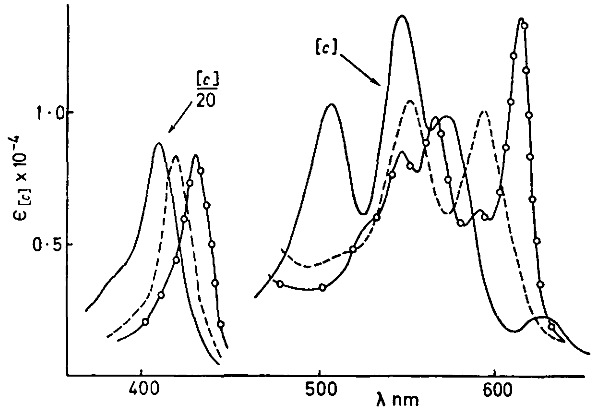

FIGURE. Visible absorption spectra in methylene chloride: ———— β-keto-ester (**1c**), — — — — (**1c**) plus two equiv. of thallium trifluoroacetate, —o—o— (**1c**) plus two equiv. of thallium trifluoroacetate followed by photolysis [*i.e.* Tl^{III} complex of (**4a**)].

When the magnesium or zinc complexes (**3b**,**c**) of the keto-ester were treated with one equivalent of thallium trifluoroacetate there was no evidence of phaeoporphyrin formation, but instead oxophlorins were produced; this has been developed into a synthesis of oxophlorins in high yield from magnesium and zinc porphyrins.[8]

It seems likely that the species obtained from the treatment of the keto-ester (**1c**) with two equivalents of thallium trifluoroacetate is the chelate (**6**) bearing an *O*-thallated keto-ester enolate. This postulate was, in part, tested by treatment of the keto-ester (**1c**) with diazomethane (2 days, 0°) to get the enol ether (**7**),† m.p. 206—208°, which would not be expected to cyclise; with two equivalents of thallium trifluoroacetate, (**7**) gave a normal *photostable* metalloporphyrin which could be readily demetallated to regenerate (**7**). It is easy to envisage photolytic decomposition of (**6**) to thallium(I) trifluoroacetate and the trifluoroacetate salt (**8**) of a thallium(III) isoporphyrin containing the carbocyclic ring; loss of trifluoroacetic acid from (**8**) would give the thallium chelate of the phaeoporphyrin (**4a**).

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§ Photolyses were carried out in Pyrex glass vessels and showed clean isosbestic points when followed spectroscopically. Oxygen was not excluded from the reaction mixtures and the process was shown to be independent of u.v. excitation by carrying out the photolyses at a wavelength of 546 nm.

¶ Treatment of authentic phaeoporphyrin-a_5 dimethyl ester with one equivalent of thallium trifluoroacetate gave an identical visible absorption spectrum.

†† The structure of this compound was confirmed by elemental analysis, visible, n.m.r., and mass spectroscopy and by mixed m.p. and comparative t.l.c. with authentic material obtained by degradation of phaeophytins.

** Presumably the yield of phaeoporphyrin in this case was relatively low as a result of the well-known instability of vinyl substituted porphyrins towards photolysis.

[1] A. H. Jackson, G. W. Kenner, S. W. McCombie, and K. M. Smith, to be published.
[2] M. T. Cox, T. T. Howarth, A. H. Jackson, and G. W. Kenner, *J. Amer. Chem. Soc.*, 1969, **91**, 1232.
[3] G. Bram and M. Vilkas, *Bull. Soc. chim. France*, 1964, 945.
[4] M. T. Cox, Ph.D. Thesis, Liverpool, 1969.
[5] K. M. Smith, *Chem. Comm.*, 1971, 540.
[6] H. Fischer and A. Stern, 'Die Chemie des Pyrrols,' Akademische Verlag, Leipzig, 1940, Vol. IIii, p. 171.
[7] Ref. 6, p. 230.
[8] S. W. McCombie and K. M. Smith, *Tetahedron Letters*, 1972, 2463.