

# Model Studies on the Type-III Porphyrin Rearrangement: Synthesis and Chemistry of Pyrrolylmethylpyrrolenines and Related Systems

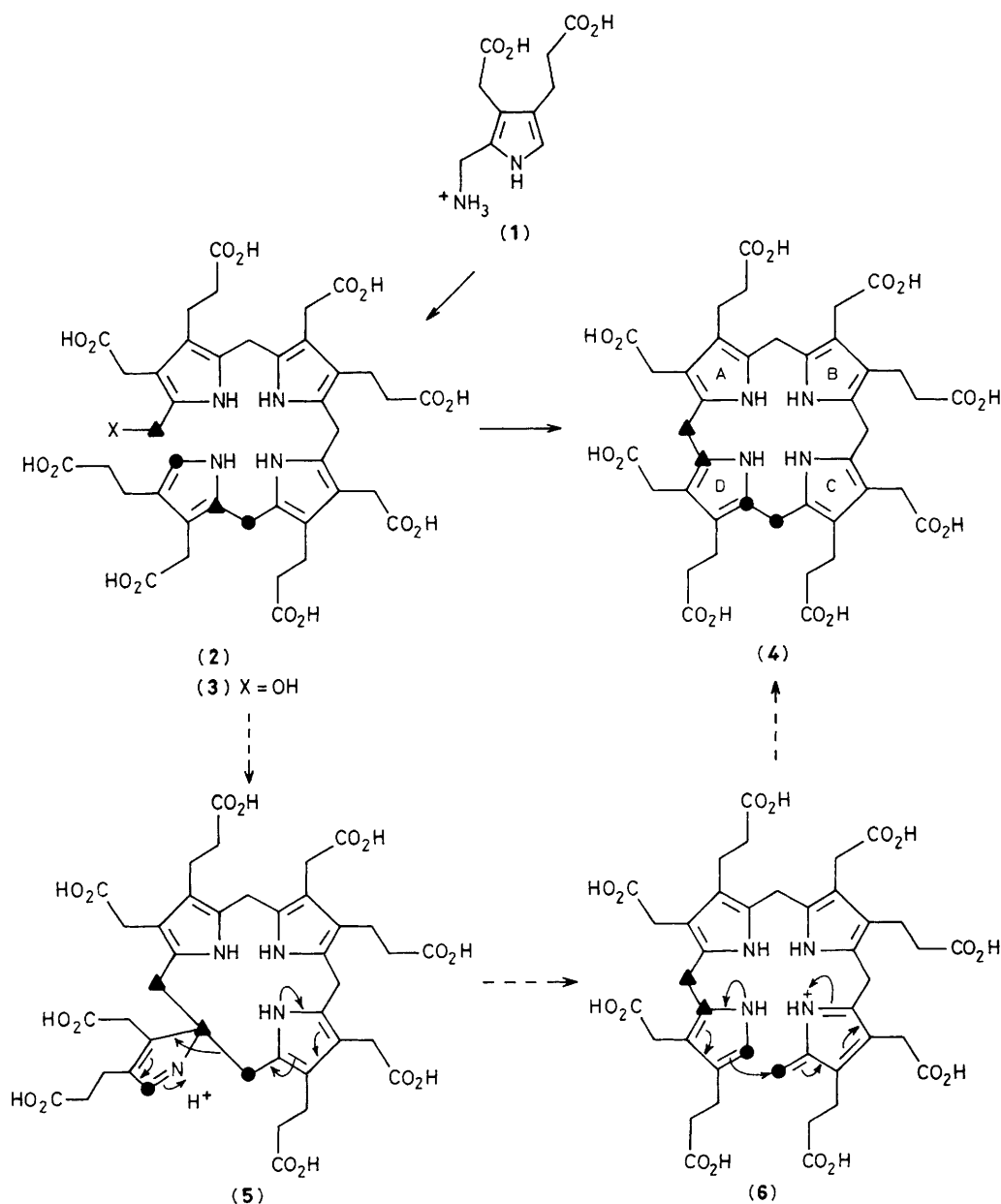
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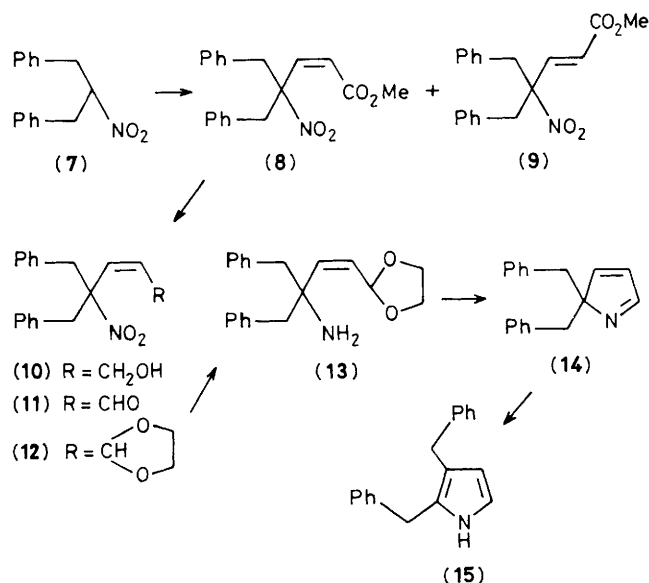
Synthetic routes to 2,2-disubstituted pyrrolenines are developed and used to construct a pyrrolylmethylpyrrolenine (**24**) of the type postulated to be an intermediate in the rearrangement which generates the natural type-III porphyrins; the synthetic system is found to undergo ready proton-catalysed rearrangement which models the proposed biosynthetic process and thus shows its feasibility.

Uroporphyrinogen-III (uro'gen-III) (**4**) is biosynthesised from porphobilinogen (**1**), PBG, by the co-operative action of two enzymes, deaminase and cosynthetase. Extensive studies have established<sup>1</sup> that (a) only the PBG unit which appears as ring D in uro'gen-III (**4**) undergoes rearrangement which is *intramolecular* with respect to that unit;<sup>2</sup> (b) the

other three PBG residues are incorporated as *intact* units;<sup>2</sup> (c) the rearrangement occurs after the linear tetrapyrrole (**2**) has been built on deaminase where the illustrated group X is a nucleophile;<sup>3,4</sup> (d) the tetrapyrrole is released from deaminase as the unrearranged hydroxymethylbilane<sup>5,6</sup> (**3**) which is ring-closed by cosynthetase with intramolecular



Scheme 1

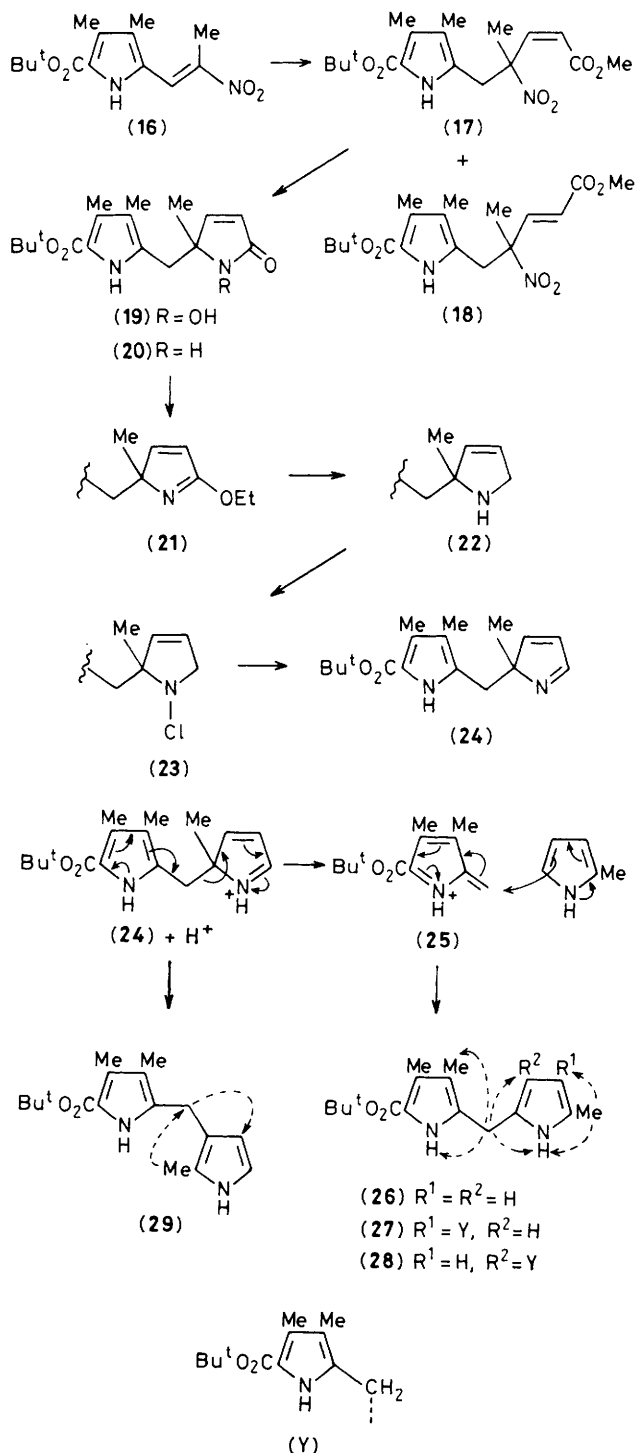


rearrangement to generate uro'gen-III (4); (e) the changes in bonding during this step are clear from the  $^{13}\text{C}$ -labelling studies<sup>3</sup> illustrated by ● and ▲ on structures (3) and (4).

Two mechanisms have been considered for the conversion of the bilane (3) into uro'gen-III (4) and which fit all these data (see ref. 5b). The one of interest for the present communication postulates that a spiro-pyrrolenine (5) is formed ready for conversion into uro'gen-III (4) either, as indicated in Scheme 1, by fragmentation to yield (6) followed by recombination or *via* a series of [1,5]-sigmatropic shifts. This possible mechanism is closely related to the early ideas of Mathewson and Corwin.<sup>7</sup> The aim of the work now outlined was to synthesise model pyrrolenines having the key features of the spiro-system (5) for studies on their possible rearrangement.

One route to 2,2-disubstituted pyrrolenines was developed for the simpler target molecule (14). Michael addition of methyl propynoate to the readily prepared nitroalkane (7) gave a separable mixture (90% yield) of the Z- and E-olefins (8) and (9) in proportion *ca.* 1:4. Reduction of (8) by diisobutylaluminium hydride (DIBAL) at 0 °C gave the alcohol (10), 98%, which was oxidised with manganese dioxide to the aldehyde (11), 81%. The derived dioxolane (12), 81%, was reduced with zinc and acetic acid at 0 °C to the amine (13), 96%, and this on *brief* treatment with hydrochloric acid in tetrahydrofuran yielded the pyrrolenine (14), 89%, m.p. 78–79 °C.

A modified approach was necessary for the pyrrolyl-methylpyrrolenine (24). The nitro-olefin (16), obtained from nitroethane and the pyrrolic aldehyde, was reduced with borohydride and the aci-nitro form so generated was directly treated with methyl propynoate to afford the Z- and E-olefins (17) and (18) in *ca.* 1:2 ratio. The Z-isomer which could be crystallised directly from the mixture in 31% overall yield was reduced by zinc and acetic acid followed by  $\text{Ti}^{\text{III}}$  chloride [to reduce the partially reduced product (19)] to yield the lactam (20), 82%. Triethyloxonium fluoroborate with 1,8-bis(dimethylamino)naphthalene converted (20) into the imino ether (21) which could be reduced at room temperature with DIBAL to the amine (22), 98%. The final steps involved N-chlorination of (22) with t-butyl hypochlorite at –20 °C to form the chloramine (23); this on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene afforded the highly sensitive pyrrolenine (24) in 20% overall yield from the amine (22).



Scheme 2

Heating a melt of the pyrrolenine (14) at 200 °C gave an essentially quantitative yield of 2,3-dibenzylpyrrole (15) presumably by [1,5]-sigmatropic rearrangement.<sup>8</sup> Also, treatment of (14) with 2% trifluoroacetic acid, TFA, in  $\text{CH}_2\text{Cl}_2$  at *ca.* 20 °C led to this same product (15), 30%, together with other unidentified material.

The rearrangements of the pyrrolylmethylpyrrolenine (24) were carried out in an inert atmosphere box (<20 p.p.m. of  $\text{O}_2$ ) using 0.05% TFA in  $\text{CH}_2\text{Cl}_2$  for 30 min at *ca.* 20 °C. Four pure products were isolated, two being dipyrroles (26),

49%, and (29), 16%, the other two being tripyrroles (27), 26%, and (28), 9%. These structures were established by mass spectrometry (including accurate mass in each case) in combination with 400 MHz  $^1\text{H}$  n.m.r. spectroscopy using the technique of nuclear Overhauser enhancement (n.O.e.) by difference.<sup>9</sup> For example, structures (26) and (29) indicate the irradiated sites (tail of dashed arrow) and sites showing a clear n.O.e. (head of dashed arrow).

The acid-catalysed conversion of the pyrrolenine (24) into the major dipyrrole (26) can be rationalised as in Scheme 2. Formation of the next most abundant product (27) and the minor one (28) is explicable by part of the major dipyrrole (26) reacting a second time with the azafulvene (25). However, such a reaction occurring on the dipyrrole (29) could also contribute to the yield of (27). Though the present results cannot rule out some rearrangement by a series of [1.5]-sigmatropic steps, the nature of the products shows that fragmentation-recombination as in Scheme 2 plays at least an important role.

The thermal rearrangement in the pyrrole series was less fully studied but at 100 °C, the pyrrolenine (24) was converted into a mixture shown by n.m.r. spectroscopy to consist mainly of the dipyrrole (26) and the tripyrrole (27).

The rapid proton-catalysed rearrangement of the pyrrolenine structure (24) into the dipyrrole system (26) exactly models the fragmentation-recombination chemistry required for the hypothetical conversion of the spiro-system (5) into uro'gen-III (4) and shows it to be feasible.

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## References

- 1 Review: A. R. Battersby, C. J. R. Fookes, G. W. J. Matcham, and E. McDonald, *Nature*, 1980, **285**, 17.
- 2 A. R. Battersby, G. L. Hodgson, E. Hunt, E. McDonald, and J. Saunders, *J. Chem. Soc., Perkin Trans. 1*, 1976, 273.
- 3 A. R. Battersby, C. J. R. Fookes, M. J. Meegan, E. McDonald, and H. K. W. Wurziger, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2786.
- 4 A. R. Battersby, C. J. R. Fookes, G. W. J. Matcham, E. McDonald, and R. Hollenstein, *J. Chem. Soc., Perkin Trans. 1*, in the press.
- 5 (a) A. R. Battersby, C. J. R. Fookes, K. E. Gustafson-Potter, G. W. J. Matcham, and E. McDonald, *J. Chem. Soc., Chem. Commun.*, 1979, 1155; (b) A. R. Battersby, C. J. R. Fookes, K. E. Gustafson-Potter, E. McDonald, and G. W. J. Matcham, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2427.
- 6 Cf. (a) G. Burton, H. Nordlöv, S. Hosozawa, H. Matsumoto, P. M. Jordan, P. E. Fagerness, L. M. Pryde, and A. I. Scott, *J. Am. Chem. Soc.*, 1979, **101**, 3114; (b) A. I. Scott, G. Burton, P. M. Jordan, H. Matsumoto, P. E. Fagerness, and L. M. Pryde, *J. Chem. Soc., Chem. Commun.*, 1980, 384.
- 7 J. H. Mathewson and A. H. Corwin, *J. Am. Chem. Soc.*, 1961, **83**, 135.
- 8 Cf. A. Laurent, P. Mison, A. Nafti, and N. Pellisier, *Tetrahedron Lett.*, 1979, 1587.
- 9 L. D. Hall and J. K. M. Sanders, *J. Am. Chem. Soc.*, 1980, **102**, 5703; *J. Org. Chem.*, 1981, **46**, 1132.