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

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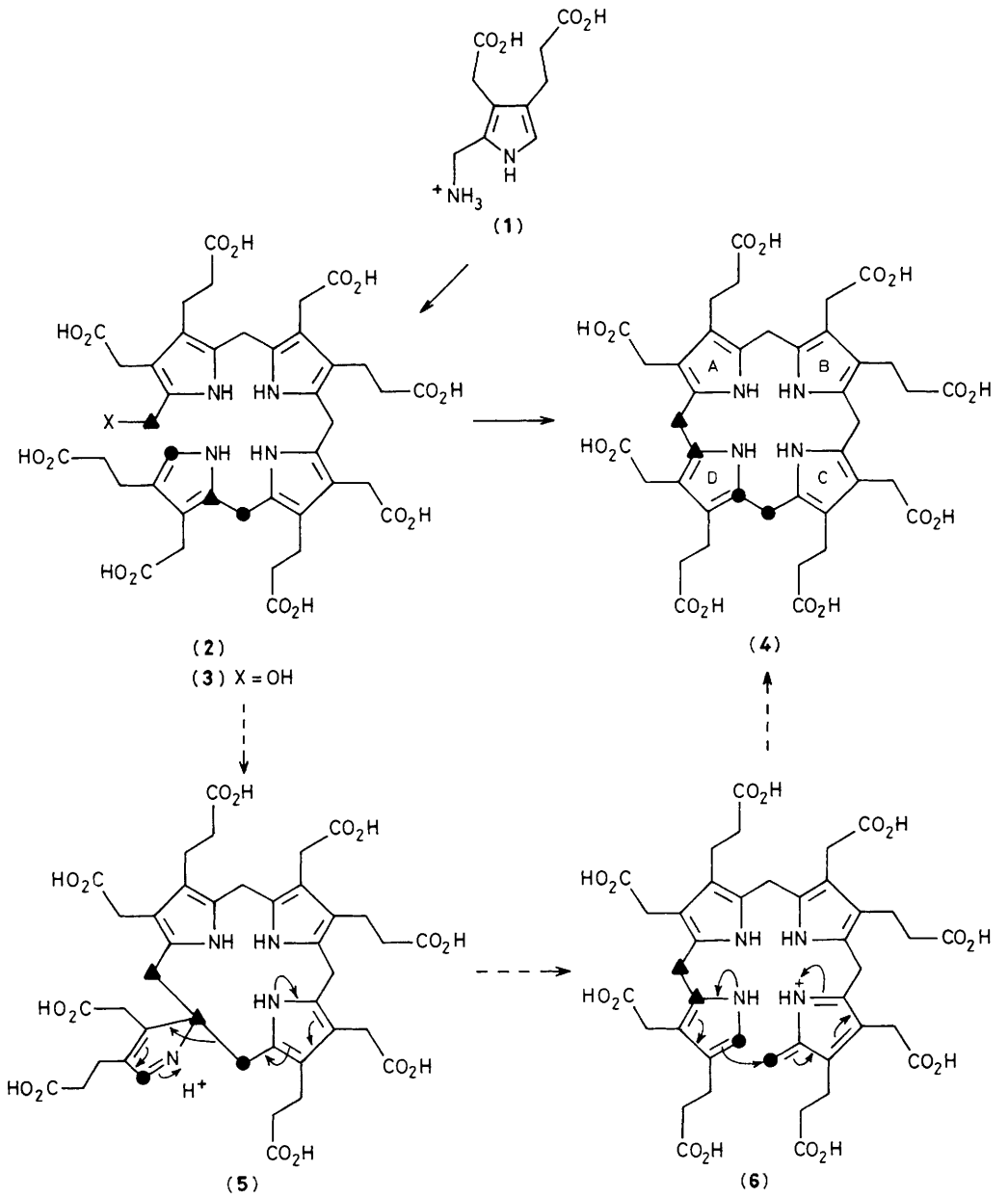
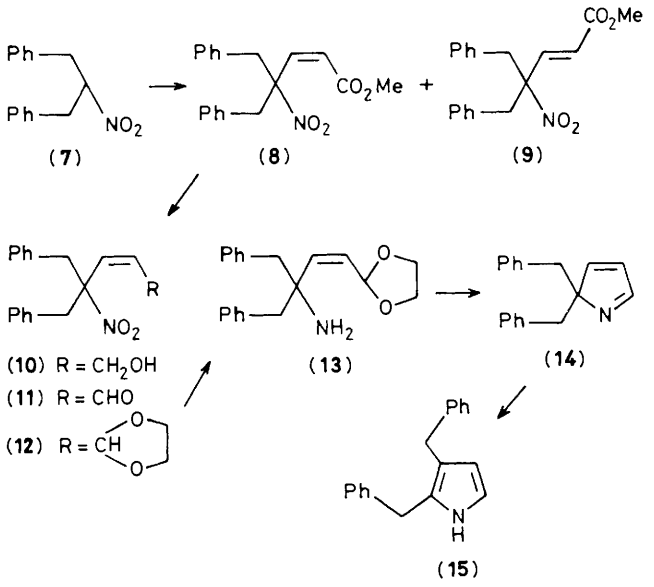
Synthetic routes to 2,2-disubstituted pyrrolenines are developed and used to construct a pyrrolylmethylpyrrolenine (**24**) of the type postulated to be an intermediate in the rearrangement which generates the natural type-III porphyrins; the synthetic system is found to undergo ready proton-catalysed 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[1] 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;[2] (b) the other three PBG residues are incorporated as *intact* units;[2] (c) the rearrangement occurs after the linear tetrapyrrole (**2**) has been built on deaminase where the illustrated group X is a nucleophile;[3,4] (d) the tetrapyrrole is released from deaminase as the unrearranged hydroxymethylbilane[5,6] (**3**) which is ring-closed by cosynthetase with intramolecular



Scheme 1

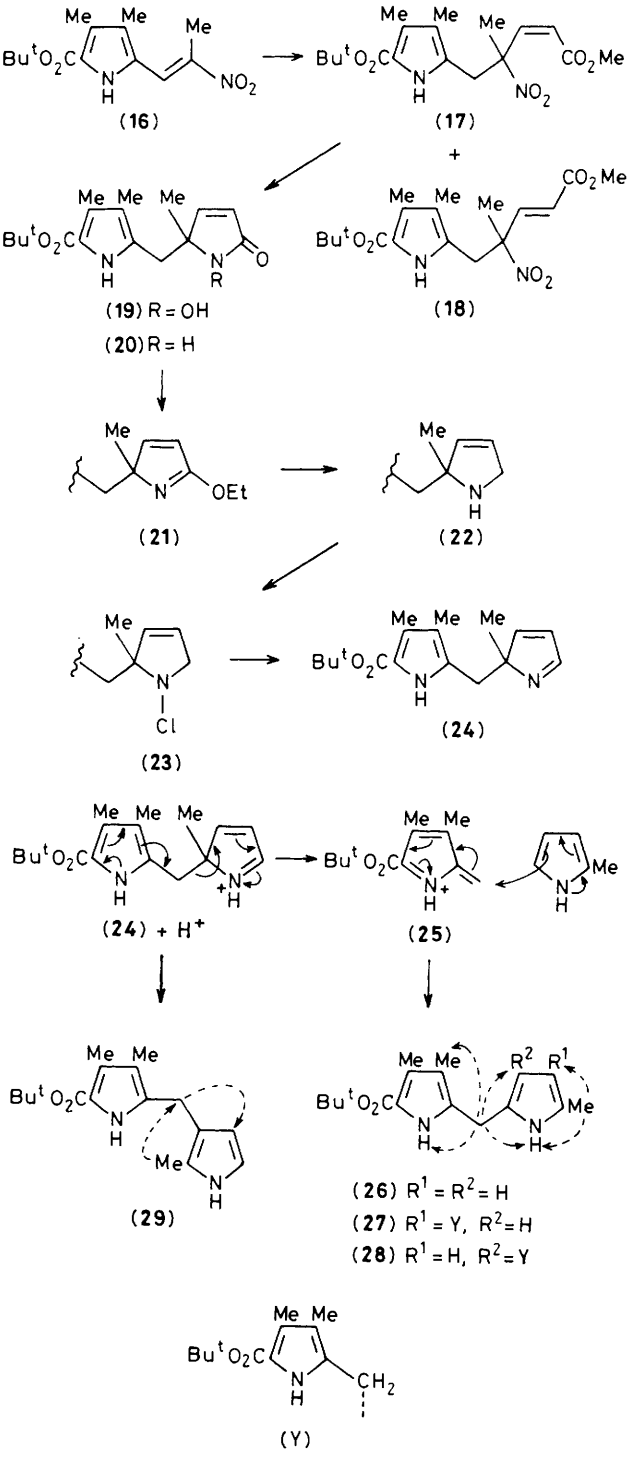


rearrangement to generate uro'gen-III (**4**); (e) the changes in bonding during this step are clear from the ^{13}C-labelling studies[3] illustrated by ● and ▲ on structures (**3**) and (**4**).

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.[7] 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 di-isobutylaluminium 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 pyrrolylmethylpyrrolenine (**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 Ti^{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.[8] Also, treatment of (**14**) with 2% trifluoroacetic acid, TFA, in CH_2Cl_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 O_2) using 0.05% TFA in CH_2Cl_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}H n.m.r. spectroscopy using the technique of nuclear Overhauser enhancement (n.O.e.) by difference.[9] 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.