Selectivity in the Rearrangement of a Di(pyrrolylmethyl)-2*H*-pyrrole

Craig J. Hawker, W. Marshall Stark, and Alan R. Battersby*

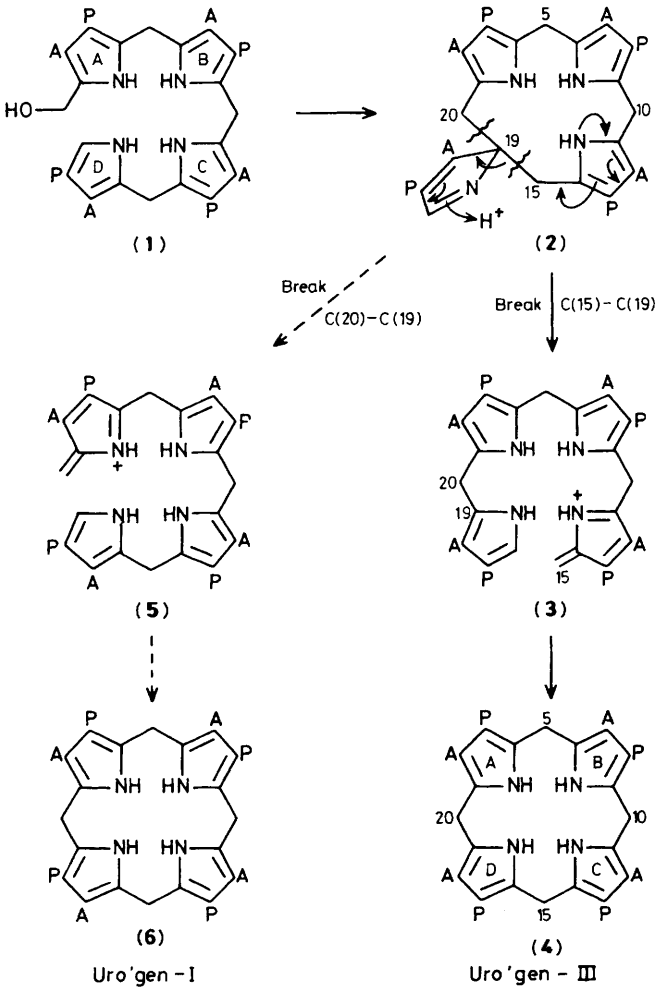
University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

A di(pyrrolylmethyl)-2*H*-pyrrole has been synthesised and its ready acid-catalysed rearrangement shows that one of the two possible modes of cleavage is preferred; this mode corresponds to that required for the formation of uroporphyrinogen-III from the putative spiro intermediate.

Uroporphyrinogen-III (**4**) (here abbreviated to uro'gen-III) is the biosynthetic parent for all the natural tetrapyrrolic pigments such as protohaem, vitamin B_{12}, and chlorophyll.[1] The last known biosynthetic intermediate before uro'gen-III is the hydroxymethylbilane[2] (**1**), which is cyclised to yield uro'gen-III with concomitant *intramolecular* inversion[3] of ring *D* and only ring *D*.[4] This remarkable conversion is catalysed by the enzyme uroporphyrinogen-III synthase (usually called cosynthetase). Recently, indirect evidence has been gained in Cambridge[5] which gives support for the putative spiro system† (**2**) acting as an intermediate for the rearrangement process (Scheme 1); the evidence was based on the strong inhibition of cosynthetase by a synthetic close analogue of (**2**).

If we accept for discussion here that the spiro system (**2**) is indeed formed and enzymically converted into uro'gen-III (**4**), it is evident that the C(15)–C(19) bond of (**2**) must break in a specific fragmentation process‡ as illustrated to give (**3**) in preference to the mechanistically equivalent C(20)–C(19) cleavage. The latter process would generate (**5**), leading to the formation of uro'gen-I (**6**). Is this selectivity entirely the result of enzymic control or is there an intrinsic preference in the non-enzymic rearrangement process for one direction of rearrangement over the other? The results of our study of this question are now outlined.

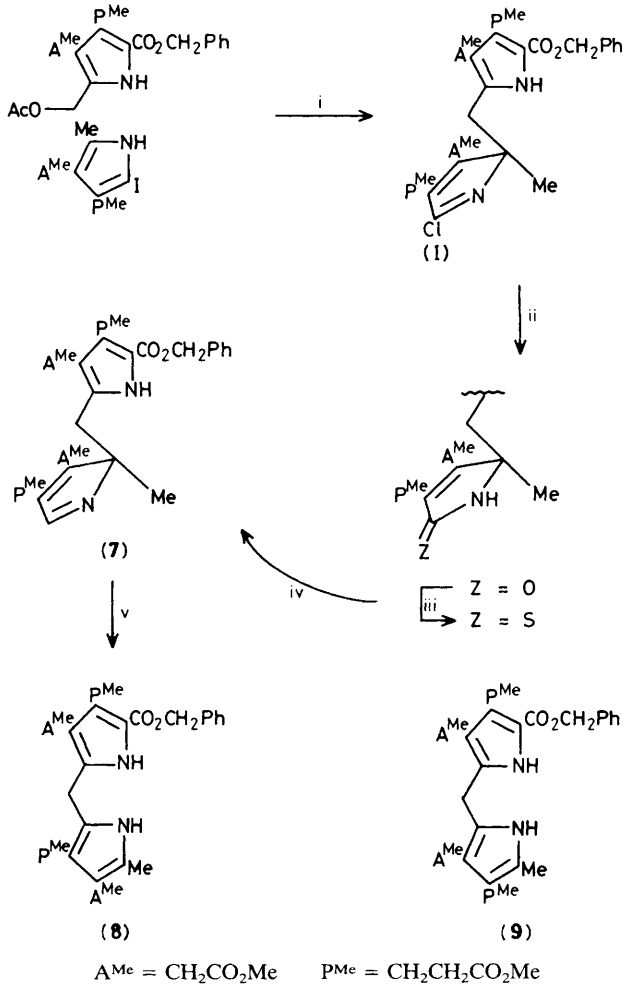
A pyrrolylmethyl-2*H*-pyrrole carrying no additional substituents on the 2*H*-pyrrole ring was known to undergo ready acid-catalysed rearrangement.[6] We first determined whether a (2,3,4-substituted pyrrolyl)methyl-2*H*-pyrrole (**7**) would similarly rearrange; this was synthesised as shown in Scheme 2. The product (**7**) was found to rearrange rapidly when treated at room temperature with 1 equiv. of toluene-*p*-sulphonic acid in dichloromethane to give the dipyrromethane (**8**) as the only product (69% yield). Structure proof involved synthesis of (**8**) and of its isomer (**9**) by unambiguous standard methods. The same single product was obtained in 39% yield



Scheme 1

† The original proposal (J. H. Mathewson and A. H. Corwin, *J. Am. Chem. Soc.*, 1961, **83**, 135) involved a heavily *C*-protonated form of the spiro system (**2**) but, nevertheless, it contained the key idea.

‡ In principle, rearrangement of (**2**) to give (**4**) could be achieved *via* three sequential 1,5-sigmatropic rearrangements. However, the chemistry reported here shows fragmentation to be important *in vitro*, so for simplicity only the one interpretation is given.

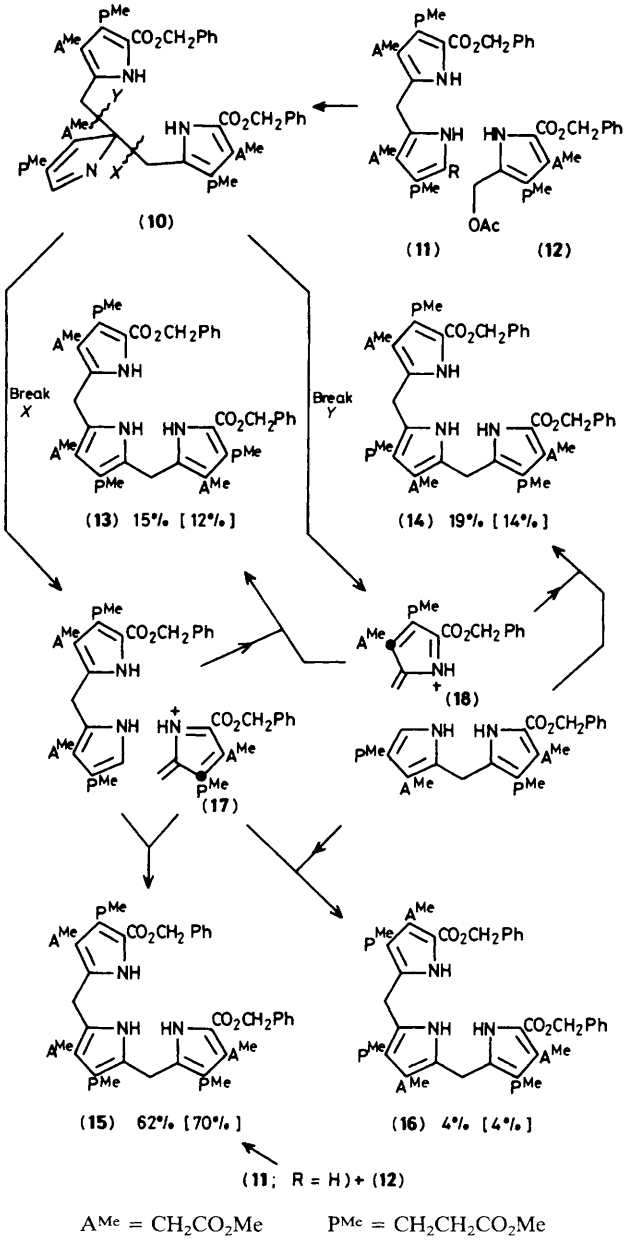


Scheme 2. *Reagents:* i, $SnCl_4$, CH_2Cl_2 (43%); ii, AgOAc, *p*-$MeC_6H_4SO_3H$, THF–H_2O (84%); iii, Lawesson's reagent (72%); iv, nickel boride, MeOH–HOAc (45%); v, *p*-$MeC_6H_4SO_3H$, CH_2Cl_2 (69%).

by rearrangement of the 2*H*-pyrrole (**7**) in boiling benzene containing 1 equiv. of *N*,*N*-tetramethyl-1,8-diaminonaphthalene.

Two competing modes of rearrangement are possible for the di(pyrrolylmethyl)-2*H*-pyrrole (**10**), which was synthesised from (**11**; R = I) and (**12**) by steps strictly analogous, and giving similar yields, to those used in Scheme 2. Acid-catalysed rearrangement of this product (**10**) as above afforded a mixture of four tripyrroles in total yield of 67%. All four products [(**13**)—(**16**)] were synthesised unambiguously by coupling a dipyrromethane [*e.g.* (**11**; R = H)] with an acetoxymethylpyrrole [*e.g.* (**12**)] in hot pyridine[7] to yield the tripyrrole [*e.g.* (**15**)]; one product was obtained in each case in 61—86% yield. These four tripyrroles were distinguishable by 400 MHz ^1H n.m.r. and were separable by h.p.l.c.; this allowed rigorous identification of the rearrangement products. The three tripyrroles, other than the minor product (**16**), were isolated in pure state from the rearrangement products for identification. The presence of the minor product (**16**) in the rearrangement mixture, and its amount, were established by n.m.r. Finally, it was established by separate experiments with the synthetic materials that all four tripyrroles [(**13**)—(**16**)] were unaffected by the mild acidic conditions used for rearrangement of the 2*H*-pyrrole (**10**).

The proportions of the four products [(**13**)—(**16**)] in the rearrangement mixture are shown as the percentages not in



Scheme 3

brackets under the relevant structures. These values showed that the rearrangement process leading to one product (**15**) (62%) had been clearly favoured over the alternative mode of fragmentation yielding (**14**) (19%). The other two products, (**13**) (15%) and (**16**) (4%) arise by crossover recombinations. When the amounts of crossover products are taken into account, one can calculate that the cleavage at *X* [see (**10**); Scheme 3] represents 70 ± 2% of the total, with the remaining 30 ± 2% being at *Y*. These values held good when the acid-catalysed fragmentation of the 2*H*-pyrrole (**10**) was run in a variety of solvents ranging from toluene to methanol. A closely similar pattern of products resulted when the 2*H*-pyrrole (**10**) rearranged in hot benzene as above (see proportions of each tripyrrole given in square brackets under structures). The total yield of tripyrroles under these conditions was 60%.

The striking aspect of these findings is that the preferred fragmentation of the 2*H*-pyrrole (**10**) at *X* corresponds to the

specific direction of cleavage and rearrangement required for the conversion of the spiro system (**2**) into uro'gen-III (**4**). A possible rationalisation for the model system (**10**) is that formation of the azafulvene (**17**) is preferred over its isomer (**18**) because the former carries a propionate residue on the δ+ carbon (•), whereas the latter has an electron-withdrawing acetate group at this centre.

We thank the Commissioners for the Exhibition of 1851 for an Overseas Scholarship (to C. J. H.), Dr. F. J. Leeper for his help, and the S.E.R.C. and Roche Products Ltd. for financial support.

Received, 29th April 1987; Com. 582

References

1 F. J. Leeper, *Nat. Prod. Rep.*, 1985, **2**, 19, 581.
2 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.
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, G. L. Hodgson, E. Hunt, E. McDonald, and J. Saunders, *J. Chem. Soc., Perkin Trans. 1*, 1976, 273.
5 A. R. Battersby, W. M. Stark and G. J. Hart, *J. Chem. Soc., Chem. Commun.*, 1986, 465.
6 A. R. Battersby, H. A. Broadbent, and C. J. R. Fookes, *J. Chem. Soc., Chem. Commun.*, 1983, 1240.
7 P. S. Clezy and V. Diakiw, *Aust. J. Chem.*, 1973, **26**, 2697.