Mechanism of the Acid-catalysed Rearrangement of α-Free Pyrromethanes

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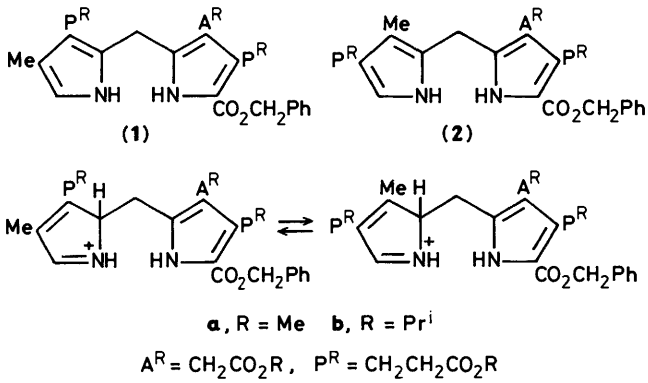
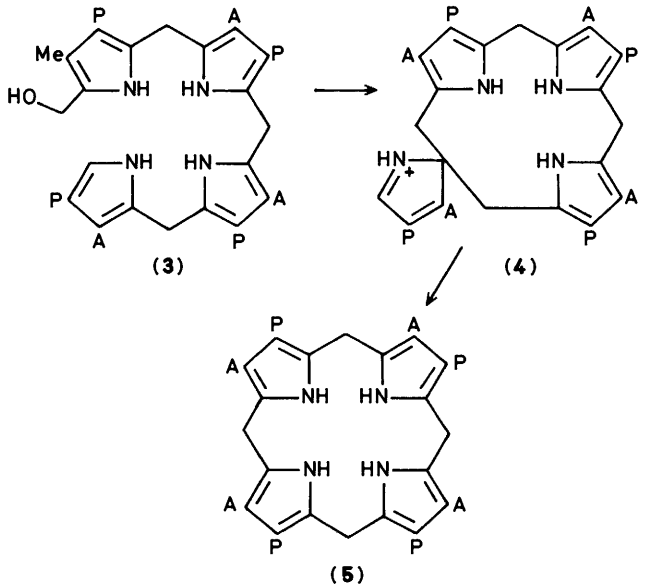
The acid-catalysed rearrangement of α-free pyrromethanes occurs by fragmentation-recombination, rather than by an intramolecular process, as shown by cross-over experiments.

During the course of porphyrin syntheses from pyrromethanes, small amounts of other porphyrinic by-products are often also formed.[1–5] The formation of these by-products has been attributed to acid-catalysed rearrangements of the pyrromethanes, and circumstantial evidence for this conclusion was provided by Mauzerall's work on the acid-catalysed isomerisation of porphyrinogens.[6] The acid-catalysed rearrangement of bilirubin-IXα to give a mixture of bilirubins-IIIα, IXα, and XIIIα is also relevant,[7] since bilirubins may be regarded as a special type of substituted pyrromethanes. More recently, we showed that the by-products in some of our *b*-oxobilane syntheses of porphyrins[8] had probably arisen by partial acid-catalysed rearrangement (*cf.* ref. 1) of α-free pyrromethane precursors, *e.g.* (**1a**) ⇌ (**2a**) as shown in Scheme 1.



Scheme 1.

An alternative mechanism for the acid-catalysed rearrangements involves an intramolecular process in which a pyrrolylmethyl residue migrates from the 2-position of the other pyrrole ring to the vacant 5-position in a series of [1,5]-sigmatropic rearrangements.[9] This type of rearrangement is also of interest in relation to the biosynthetic cyclisation of the tetrapyrrolic hydroxymethylbilane precursor (**3**) of uroporphyrinogen-III (**5**) which is thought[10] to occur *via* the spirocyclic intermediate (**4**) (Scheme 2). It has also been



Scheme 2.

suggested that rearrangement of the latter might occur by either (*a*) a fragmentation-recombination process, or (*b*) by a series of [1,5]-sigmatropic migrations.[11,12] In the case of bilirubins,

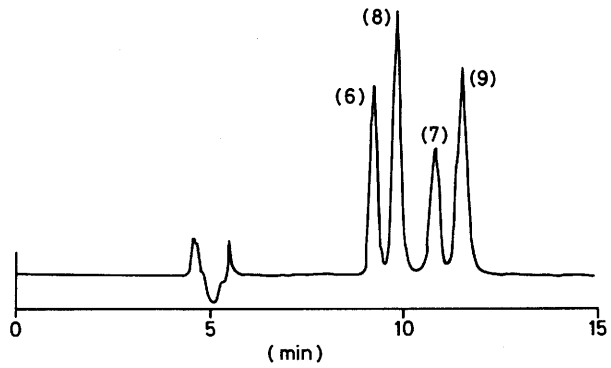
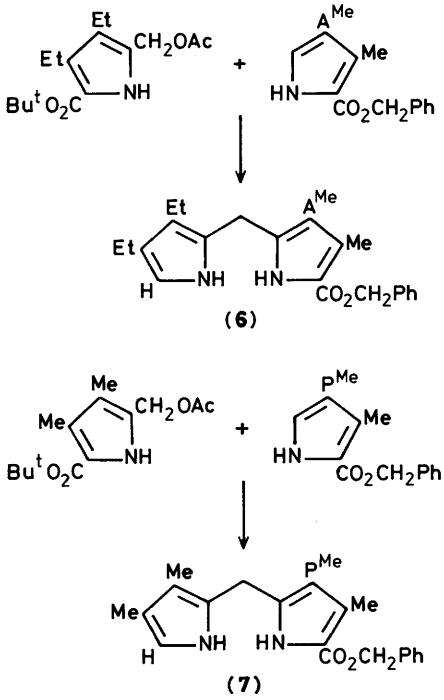


Figure. H.p.l.c. analysis of the mixture of pyrromethanes formed from (**6**) and (**7**) after treatment with trifluoroacetic acid [5 μ Hypersil, 4.5 mm × 250 mm; solvent, ethyl acetate–hexane: 15:85 (v/v) at 1 ml/min, u.v. detector set at 280 nm].

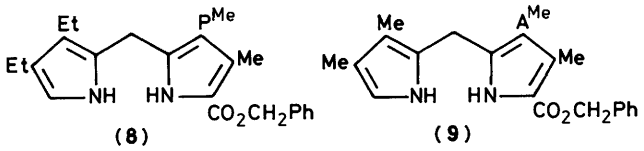
referred to above, the rearrangements also occur by a fragmentation-recombination process as shown by cross-over experiments.[13]

In the present paper we now provide direct evidence that pyrromethanes will undergo acid-catalysed isomerisation, and show that the mechanism involves a fragmentation-recombination process. Initially, we carried out preliminary studies of cross-over experiments involving simultaneous rearrangement of the α-free pyrromethane trimethyl ester (**1a**) and the analogous α-free pyrromethane tri-isopropyl ester (**1b**), but the mixture of products obtained was too complex to separate satisfactorily. (Eight pyrromethanes can, in theory, be formed by rearrangement and fragmentation.) For these reasons, we synthesized the two new α-free pyrromethanes (**6**) and (**7**) each of which had identical β-substituents on the α-unsubstituted pyrrole ring. These were prepared by condensation of an α-acetoxymethylpyrrole benzyl ester with an α-free pyrrole t-butyl ester, followed by trifluoroacetic acid catalysed de-esterification and decarboxylation of the resulting pyrromethane t-butyl ester as shown in Scheme 3. An equimolar



Scheme 3.

mixture of the two α-free pyrromethanes was then subjected to simultaneous rearrangement in the presence of 0.1 mol equiv. of trifluoroacetic acid in dichloromethane at 25 °C for 1 h. After work-up, field desorption mass spectrometry of the crude reaction product and h.p.l.c. analysis (Figure) showed the presence of the starting materials (**6**) and (**7**), and slightly larger amounts of the two cross-over products (**8**) and (**9**). The



new products were identified by comparisons with authentic materials, each of which was synthesized in a similar manner to pyrromethanes (**6**) and (**7**).

This result provides clear evidence not only that α-free pyrromethanes undergo acid-catalysed isomerisations, but also that the chemical process involves a fragmentation-recombination type of mechanism. It also accords with the conclusions reached in recent model studies[11] related to the biosynthetic formation of uroporphyrinogen-III (**5**) from the putative spirocyclic intermediate (**4**), *i.e.* that the acid catalysed or thermal rearrangement of a 2,2-disubstituted pyrrolenine also occurred (at least in part) by a fragmentation-recombination process. Both these results, and our own findings, suggest that the natural process (Scheme 2) also involves a fragmentation/recombination. In contrast to previous studies of rearrangements of pyrromethanes, or systems containing pyrromethane units (*e.g.* porphyrinogens or bilirubins) our studies show specifically that pyrromethanes with one α-position unsubstituted undergo acid-catalysed rearrangement by fragmentation-recombination to afford pyrromethanes with inversion of the α-free pyrrole ring.

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